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American Heart Journal

VOL. 50 SEPTEMBER, 1955 No. 3

Original Communications

DIAGNOSIS OF SYPHILITIC CARDIOVASCULAR DISEASE WITH SPECIAL REFERENCE TO TREPONEMAL IMMOBILIZATION TESTS

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IT IS well known that late manifestations of cardiovascular syphilis may be present in patients whose blood fails to give positive reactions in the serologic tests for syphilis. These tests depend on the presence of reagin in the blood although the antigens employed in modern techniques are not specific in the usual immunologic sense. The treponemal immobilization test (TPI) introduced by Nelson and Mayer[1] detects the presence of antibodies that are independent of reagin. They would appear to be useful in differential diagnosis in subjects with negative standard serologic tests but with cardiovascular lesions suspected of being syphilitic. Indeed isolated instances of this type have been reported.[2-4]

The present report deals with observations on TPI tests in thirty-three individuals with lesions of the aorta or aortic valves and in whom standard serologic tests for syphilis were either negative or weakly reactive. Some were known syphilitics and others had no corroborative evidence for the existence of syphilis. In every one the question of syphilitic cardiovascular disease was prominently raised in differential diagnosis. One patient had an aneurysm of the abdominal aorta, one had calcification of the ascending aorta. All of the others had murmurs of aortic insufficiency either alone or with stenosis.

The cases were classified into three groups based on the clinical impression as to the etiology of the disease (1) syphilitic, (2) nonsyphilitic, (3) unknown or uncertain cause. All of the subjects in the syphilitic group (Table I) had aortic insufficiency with or without an aneurysm but not accompanied by stenosis or calcification of the valve. All but two had a history of infection at least 25 years earlier and previous positive serologic tests or treatment for syphilis. With one exception subjects in this group had received no antiluetic treatment or very inadequate treatment during the first two years of their infection. One patient (W.C.) gave a history of having received 20 to 30 intramuscular and intravenous injections within the first four years following a penile lesion.

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TABLE I. ETIOLOGY SYPHILITIC

CASE	AGE	DURATION OF SYPHILIS (YR.)	SPINAL FLUID KOLMER	SEROLOGIC BLOOD TESTS					REMARKS
				KOLMER MCKINNEY	KOLMER CHAMBLEE	KAHN	VDRL	TPI	
FW	64	37	Neg	Neg	1	Neg	Neg	Neg	AI*; calcification of ascending aorta
WJ	63	?	Neg	Neg	Neg	Neg	Neg	Neg	AI; unilateral optic atrophy of unknown cause
DW	66	40	Neg	Neg		Neg	Neg	Neg	AI; hypertension labile
WC	56	31		Neg	Neg	Neg	1	Pos	AI; received 15 million units penicillin, 1952-1954
CC	58	43	Neg	Neg	1	Neg	Neg	Pos	AI; some "606" in 1920
RA	51	33	Neg	Neg	Neg	Neg	Neg	Pos	AI; hypertension, 210/110 mm. Hg
RJ	57	37		Neg	Neg	Neg	Neg	Pos	AI
BC	63	36	Neg	Neg	Neg	Neg	Neg	Pos	AI and aneurysm of aorta; 9 million units of penicillin 1 yr. before TPI
VA	65	27	Doubtful	Neg	1	Doubtful Neg	Less than 1	Pos	AI; tabes dorsalis; 9 million units penicillin prior to TPI test
EJ	64	44	Neg	Neg	Neg	Neg	Neg	Pos	AI; unknown amount of penicillin 6 yr. before and 9 million units 7 months prior to TPI test
HR	53	39	Neg	Neg	Neg	Neg	Neg	Pos	AI; penicillin 9.0 million units in 1949 and 6.0 million units in 1954
HM	59	?	Neg	Neg	Neg	Neg	Neg	Pos	AI; received 40 million units between 1947 and 1954.

*AI = aortic insufficiency.

The group judged clinically to be nonsyphilitic (Table II) includes seven patients with rheumatic aortic valvular disease, three with functional aortic insufficiency associated with hypertension, one with arteriosclerotic aneurysm of the aorta and one subject with calcification of aortic ring. None had clinical or serologic evidence of syphilis. Three were comparatively young, the ages being 29, 33, and 35 years. One (V.C.) had calcification of the aortic valve and one (W.F.), aged 64, had a diastolic murmur which developed shortly following an episode of fever and carditis. Two individuals had rheumatic aortic stenosis and insufficiency but were included here because in both cases (R.L. and T.H.) there was a history of syphilis in the past. In both instances the syphilitic infection was adequately treated and apparently arrested. Nevertheless, the knowledge of the existence of syphilis in the past raised the question of the presence of combined syphilitic and rheumatic aortic valvular disease.

TABLE II. ETIOLOGY NONSYPHILITIC

CASE	AGE	SEROLOGIC TESTS OF BLOOD				DIAGNOSIS
		KOLMER	KAHN	VDRL	TPI	
JK	29	Neg	Neg	Neg	Neg	Rheumatic AI*
RL	64	Neg	Neg	Neg	Neg	Rheumatic aortic stenosis and insufficiency; syphilis late latens—apparently arrested—22 yr. duration
TH	63	Neg	Neg	Less than 1	Neg	Rheumatic aortic stenosis and insufficiency; mitral insufficiency; history of previously treated syphilis, 40 yr. duration
HC	61	Neg	Neg	Neg	Neg	Hypertension; functional AI
CP	58	Neg	Neg	Neg	Neg	Hypertension and arteriosclerotic heart disease; Arteriosclerosis of aorta; functional AI
WH	60	Neg	Neg	Neg		Arteriosclerotic aneurysm of abdominal aorta
WB	76	Neg	Neg	Neg	Neg	Calcification of aortic ring with AI
DJ	59	Neg	Neg	Neg	Neg	Hypertension (250/130 mm. Hg); functional AI
RW	33	Neg	Neg	Neg	Neg	Rheumatic AI
WF	64	Neg	Neg	Neg	Neg	Rheumatic AI; arteriosclerotic coronary disease
VC	60	Neg	Neg	Neg	Neg	Rheumatic AI; calcification of aortic valve
RP	35	Neg	Neg	Neg	Neg	Rheumatic AI

AI = aortic insufficiency.

A third category consisted of nine individuals with aortic diastolic murmurs that could not be readily attributed to syphilitic or nonsyphilitic causes. Histories of syphilis or rheumatic fever were not elicited. Hypertension was noted in three of the patients but in only one of these was the intensity of the murmur related to the level of blood pressure. Brief protocols are recorded below.

CASE REPORTS

CASE 1.—M.J., a 65-year-old Negro farmer was admitted with symptoms of headache and dizziness of 2 years' duration and shortness of breath for 10 to 12 years. The findings were moderate cardiac enlargement, hypertension, the blood pressure level being in the range of 200/100 mm. Hg. The aortic second sound was loud and tambour in quality, and there was a well-defined,

blowing diastolic murmur varying in intensity with the level of blood pressure from faint to Grade 2. The aorta showed no evidence of calcification in the ascending portion nor any evidence of aneurysm on x-ray. He recalled a penile lesion while in the Army in 1918 but received no specific treatment and was not aware of any positive serologic tests or other manifestations of syphilis at any time. Kolmer, VDRL, and Kahn tests of the blood were negative; TPI test was positive. The clinical impression was that he had hypertensive heart disease with a functional aortic insufficiency. Syphilitic aortic insufficiency could not be excluded.

CASE 2.—W.R., a 64-year-old Negro had been known to be hypertensive for at least 12 years. The blood pressure levels have ranged between 230/150 and 150/90 mm. Hg. In 1951, a diastolic murmur was heard in the aortic area. This murmur would be present only at the high levels of blood pressure and could not be heard at lower levels. In 1954, the murmur was again heard about Grade 2 in intensity and accompanied by a Grade 1 systolic murmur. There was no clear-cut history of syphilis, although he stated that at the age of 14 he had gonorrhea and a penile lesion. He was somewhat disoriented mentally, and the history could not be considered reliable. Blood and spinal fluid serologic tests were negative on repeated occasions. A diastolic murmur was heard with blood pressures as low as 180/100 mm. Hg. It was considered that he had hypertensive cardiovascular disease with cardiac enlargement. The possibility of coexistence of syphilitic aortitis and aortic insufficiency could not be ruled out. The tests at Chamblee, Georgia, showed negative Kolmer and VDRL reactions but positive TPI tests.

CASE 3.—E.H., a 57-year-old Negro was first admitted to this hospital in June, 1950, because of rash on the hand due to epidermophytosis. On incidental examination the heart was found to be enlarged. There was a Grade 2 blowing systolic and a Grade 3 blowing diastolic murmur in the aortic area, transmitted down the sternum. The aorta showed moderate elongation and tortuosity with some diffuse dilatation of the arch. The blood serologic tests for syphilis were negative. He denied all knowledge of previous syphilis, positive tests, or treatment. The etiology of the heart disease was in doubt, but, nevertheless, he did receive 6,000,000 units of penicillin. One year later he was again examined and at this time a mitral presystolic murmur was found and was considered to be an Austin Flint murmur. The blood pressure was 120/60 mm. Hg. In 1954, he showed the same cardiac findings with the blood pressure being recorded as 170/50 mm. Hg. Blood Kolmer, Kahn and VDRL tests for syphilis were again negative. The TPI test was positive. In view of the positive test the diagnosis was changed to syphilitic heart disease and aortic insufficiency.

CASE 4.—R.S., a 58-year-old Negro, was first seen at this hospital in June, 1950, with symptoms of tachycardia, dyspnea and precordial pain. He had unmistakable evidence of thyrotoxicosis. In addition, he had a slightly enlarged heart with a Grade 2 to 3 systolic and a Grade 2 diastolic murmur in the aortic area. Blood pressure was 140/70 mm. Hg. Precordial pain was of two types, one of 4 years' duration, definitely related to exertion and believed to be angina pectoris. Another was of 10 to 11 years' duration, more or less of a burning type and not related to effort. The basal metabolic rate was +46. Subtotal thyroidectomy was performed with marked but not complete remission of symptoms and evidence of thyrotoxicosis. The aortic diastolic murmur persisted and has been recorded on repeated observations when the patient was in euthyroid state. The pulse pressure has been usually around 50 to 60 mm. Hg, the blood pressure at the level of 140/80 mm. Hg. He gave a history of having had a penile lesion while in the Army but denied specific knowledge of previous positive serologic tests or specific treatment for syphilis. On each of his four visits between 1950 and 1954 the blood Kolmer and Kahn tests were negative. The spinal fluid serology was negative. On the basis of clinical suspicion the patient received 9 million units of penicillin in 1952 and again 9 million units in November, 1954, the last dose being taken on the day the blood samples were drawn for the TPI test. The TPI reaction was positive; blood Kolmer and VDRL on the same sample were negative.

CASE 5.—A.R., a 64-year-old Negro, was admitted in February, 1954, in severe congestive failure and acutely ill. He had been treated by his private physician for known heart disease for a period of about 5 years. The findings on admission were, in addition to congestive heart failure, a huge heart with predominant left ventricular enlargement, a systolic and a well-defined diastolic murmur in the aortic area, and a systolic as well as a different (lower-pitched) type of diastolic murmur in the mitral area. Blood pressure was 140/90 mm. Hg. There was no evi-

dence of unusual dilatation of the aorta or of the left auricle. There was no calcification within the heart chamber. There was no history of syphilis or previously known positive serologic tests or treatment for syphilis, nor was there a definite history of rheumatic fever. He improved on the usual regimen for congestive failure. Blood and spinal fluid serologic tests for syphilis were negative. TPI test was negative. The clinical impression was heart disease of unknown etiology—probably rheumatic—aortic stenosis and insufficiency, mitral stenosis and insufficiency.

CASE 6.—D.L., a 36-year-old white man, was admitted to the hospital March, 1954, with a history of dyspnea and congestive failure a year before admission, and knowledge of hypertension for about two years. Physical examination revealed elevated blood pressure, 160/108 mm. Hg, moderate cardiac enlargement, systolic and diastolic murmurs in the aortic area, and a harsh Grade 3 systolic murmur in the mitral area. There was no history of syphilis or of rheumatic fever. The blood Kahn and Kolmer reactions were negative. The spinal fluid was perfectly normal. Fluoroscopic and x-ray examinations showed a normal aorta but a definitely enlarged heart. Tests done at Chamblee, Georgia, showed Kahn 1 unit, VDRL and TPI negative. The clinical diagnosis was hypertensive cardiovascular disease and valvular heart disease of unknown etiology.

CASE 7.—W.D., a 58-year-old white man, was admitted in June, 1953, for symptoms of a duodenal ulcer. On routine examination evidence of aortic insufficiency was discovered with slight cardiac enlargement and well compensated heart. The blood pressure was 170/60 mm. Hg. There was no history of syphilis. The serologic tests of the blood were negative. Spinal fluid was not examined. There was a history of a febrile illness in the late teens, the nature of which was not known to him, but at no time did he have a clear cut episode of rheumatic fever. The diagnosis was aortic insufficiency of unknown etiology. TPI tests were negative.

CASE 8.—S.W., a 56-year-old white man, was admitted to this hospital in April, 1953, complaining of dysphagia of 4 to 5 years' duration. He was found to have an esophageal stricture and a periesophageal hiatus hernia. On routine examination there was elongation and well-defined calcification of the ascending thoracic aorta. Because this finding is often seen in syphilitic aortitis, he was carefully examined for evidence of syphilis but none was found, either by history, serologic tests, or physical examination. TPI tests were negative. The clinical diagnosis is arteriosclerosis of the ascending aorta with calcification.

CASE 9.—O.S., a 41-year-old white man, has had retrosternal chest pain for a period of at least 11 years. Dyspnea on exertion and impaired physical reserve were present for an indefinite time. He has physical signs of a free aortic insufficiency and, in addition, an aneurysm of the ascending aorta. He had marked cardiac enlargement and evidence of myocardial insufficiency. The etiology for the cardiovascular disease was not clear cut. There was no history of syphilis, previous positive serologic tests, or specific antiluetic treatment. There was no history of rheumatic fever except that of a febrile illness of unknown cause at the age of six years. The final diagnosis was valvular heart disease of the aorta and aneurysm of the aorta of unknown etiology. TPI tests were reported as negative. The Kahn and Kolmer tests at this hospital were entirely normal on three separate occasions.

RESULTS

The results are summarized in Table III. Of the twelve patients in the syphilitic group the TPI tests were positive in nine and negative in three. Six of the nine subjects with positive TPI tests had negative standard serologic tests and three had small amounts of reagin which gave doubtfully positive but discordant reactions in some tests. It is noteworthy that treponemal immobilizing antibodies persisted for long periods, ranging from 26 to as long as 44 years after initial infection. Treatment with penicillin in doses of 9 to 40 million units within months to years prior to the sampling of blood for the TPI test did not prevent a positive reaction in six instances.

In the group with aortic valvular lesions of uncertain etiology four had positive and five negative TPI tests. None of the four patients with demonstra-

TABLE III. TPI TESTS IN PATIENTS WITH NEGATIVE OR WEAKLY REACTIVE COMMON TESTS FOR SYPHILIS

ETIOLOGY OF LESION	NO. CASES	COMMON SEROLOGIC TESTS		TPI TESTS	
		NEGATIVE	DOUBTFUL	POSITIVE	NEGATIVE
Syphilitic	12	9	3	9	3
Nonsyphilitic	12	12	0	0	12
Uncertain	9	8	1	4	5

ble immobilizing antibody had clinical evidence of syphilis by history, commonly used serologic tests for syphilis, or physical signs apart from the aortic insufficiency.

No positive TPI reactions were found in the patients whose disease was judged clinically to be nonsyphilitic in origin. This was true in the two individuals with aortic stenosis and insufficiency and a history of treated syphilis in the past.

DISCUSSION

The most common manifestations of cardiovascular syphilis are aortitis, aortic insufficiency, aortic aneurysm, and coronary ostial stenosis. None of these pathologic conditions gives symptoms and physical signs which are sufficiently unique to permit an unqualified etiologic diagnosis of syphilis in the absence of some other evidence of syphilis. Uncomplicated aortitis is extremely difficult to diagnose during life with any degree of accuracy. In most instances it is a pathologic and not a clinical entity. Aortic insufficiency without stenosis may be due to rheumatic fever, congenital and degenerative valvular deformities, and bacterial endocarditis. Aneurysms of the aorta may be arteriosclerotic or congenital in origin. Unperforated dissecting aneurysm of the aorta not uncommonly gives a clinical picture which closely simulates an aneurysm with aortic insufficiency and coronary ostial involvement. The symptoms of coronary insufficiency due to ostial stenosis cannot readily be distinguished from those due to arteriosclerotic coronary disease.

It must be emphasized that known syphilitics do have cardiovascular lesions that are in fact nonsyphilitic in etiology but resemble those due to the treponema pallidum. Individuals with congenital or degenerative lesion may develop syphilis, and there is no cross immunity between syphilis and rheumatic fever. Furthermore, instances of the coexistence of rheumatic and syphilitic heart disease have been documented.[5] The finding of a positive blood test or TPI reaction in a person with aortic insufficiency, angina pectoris or aneurysm does not necessarily mean that syphilis is the cause of the cardiac abnormality. Nor does a negative reaction exclude the possibility of the presence of lesions of late syphilis. Three of our patients suspected of having syphilitic aortic insufficiency had negative TPI tests. One of them (F.W.) had a history of syphilis of 37 years standing, a weak Kolmer reaction (1 unit) in one test and calcification of the ascending aorta. The evidence strongly favors syphilitic etiology for

the valvular disease despite the negative TPI test. The second patient (D.W.) had a history of untreated infection of 40 years standing. The ascending aorta showed slight dilatation and calcification. There was labile hypertension and the diastolic murmurs persisted even at lower levels of blood pressure. In this instance also the probability of syphilitic aortic insufficiency is high. The third subject (W.J.) had no history of previous infection or treatment. The only additional evidence in favor of syphilis was the presence of unilateral optic nerve atrophy of unexplained origin. The diagnosis of syphilitic etiology for the heart disease in this case rests on tenuous ground and may be in error. In the group with heart disease of unknown or uncertain cause there were five negative TPI tests. Three of these affections may conceivably be syphilitic in origin although one (W.L.) is of an age (36) seldom encountered at this hospital among military veteran patients with cardiovascular syphilis. One patient (S.W.) had calcification of the ascending aorta without valvular disease. This finding is not incompatible with atherosclerosis of the aorta. The fifth individual (A.R.) had murmurs suspicious of rheumatic mitral as well as aortic disease. By auscultation alone the murmur of organic mitral stenosis cannot be distinguished from the Austin Flint murmur heard not infrequently in syphilitic aortic insufficiency. We have never encountered an Austin Flint murmur except in conjunction with free aortic regurgitation and a pulse pressure of at least 60 mm. Hg. Peripheral signs of a free aortic insufficiency were not prominent in subject A.R., and we believe the mitral murmur to represent organic mitral disease rather than an Austin Flint murmur in this instance.

Two hundred male patients with cardiovascular syphilis were observed at the Veterans Hospital during the 8 year period following 1946. They ranged in age from 21 to 72, the mean being 56 years. The duration of syphilitic infection was known in 108 instances and averaged 31 years with a range of 11 to 50 years. The extent of early antisyphilitic therapy could be estimated in 151 subjects. Ninety-three per cent of these individuals had had very little or no antisyphilitic therapy within the first two years of the infection and only 7 per cent had had ten or more injections of arsenical preparations.

Thus, it would appear that the characteristic background history of a person with cardiovascular syphilis is treponemal infection of at least 10 years standing and usually longer with little or no specific treatment during the first two years. These findings are in accord with those reported by previous observers.[5]

The serologic tests in the blood (Kolmer and Kahn) were positive in 142, negative in forty-six and doubtful in ten instances. Collateral evidence of syphilis was present in most of the fifty-six patients with negative or doubtful serologic blood tests. Thus, eleven individuals had central nervous system syphilis. One had a history of syphilis and a perforated nasal septum, and in thirty-three there was a history of infection and previous positive tests or specific treatment. In only eleven instances was there no history or evidence of syphilis independent of the cardiac findings.

Seven additional cases not included in the 200 described above are of particular interest in this connection because erroneous diagnoses of syphilitic cardiovascular disease were made. In six of the seven instances there was no

collateral evidence of syphilitic infection. At necropsy two of these subjects had rheumatic aortic valvulitis, one had dissecting aneurysm of the aorta, and two showed no evidence of valvular or aortic disease. A sixth patient still living had signs of pure aortic insufficiency when first seen. In the course of time he has developed definite evidence of aortic stenosis and calcification of the aortic valve, findings which render untenable the previously postulated syphilitic valvular disease. These observations indicate the degree of error that attends the diagnosis of syphilitic etiology for a cardiac lesion unattended by collateral evidence of syphilis.

In most instances the existence of syphilis can be corroborated either by past history of infection, by positive serologic tests or by findings of late lesions apart from the heart and aorta. In a small number of syphilitic suspects none of these collateral evidences will be elicited. It is in that group that the TPI test should be most useful. This is exemplified in the group of individuals with aortic insufficiency of unknown etiology. Four of the nine patients in this category had positive TPI reactions as the only corroborative evidence of syphilis.

SUMMARY

1. Treponemal immobilizing antibodies have been detected in the blood of reagin-free subjects with late manifestations of cardiovascular syphilis 26 to 43 years following the initial infection.

2. The treponemal immobilizing test is of definite help in establishing the existence of syphilis in individuals with negative serologic tests commonly employed.

3. A large margin of error may attend the diagnosis of cardiovascular syphilis in patients in the absence of collateral evidence of syphilitic infection.

SUMMARIO IN INTERLINGUA

1. Anticorpores que immobilisa treponema esseva detegite in le sanguine de individuos sin reagina qui exhibiva tardive manifestationes de syphilis cardiovascular inter 26 e 43 annos post le infection initial.

2. Le test de immobilisation de treponema es clarmente de adjuta in establir le diagnose de syphilis in individuos monstrante negative reactiones in le currente tests serologic.

3. In le absentia de signos collateral de infection syphilitic le diagnose de syphilis cardiovascular es characterisate per un alte grado de fallibilitate.

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CARDIAC ENLARGEMENT OF UNDETERMINED CAUSE IN ASYMPTOMATIC ADULTS

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IT IS a commonly accepted premise that an enlarged heart is a diseased heart. An exception has been raised from several sources regarding the so-called "athletic heart,"[1,2] but even this has been denied by others.[3] Several methods of evaluating cardiac size in the living have been proposed. Regardless of which procedure one uses, the criteria are subject to criticism, particularly with respect to borderline or slight enlargement. The simplest and probably the most widely employed method is that of Ungerleider and Clark.[4] They established standards for adults, based on height and weight, utilizing the transverse cardiac diameter measured on the teleroentgenogram. They concluded that a cardiac diameter which is more than 10 per cent greater than the predicted value should be regarded as abnormal, and that the heart may be considered as almost certainly enlarged if this increment is over 15 per cent. The limitations and pitfalls of this and all other methods of cardiac mensuration have been recognized.[5,6] These include radiologic technique factors, poor visualization of the cardiac border caused by motion, epicardial fat pad or elevated diaphragm, allowance of too high values in obese individuals, and failure to identify enlargement of initially small hearts. Nevertheless, Wittenborg and Sossman[5] found that this method yields good correlation with clinical heart disease and confirmed that an increase in size of 11 per cent or more is probably abnormal, and that an increase of 15 per cent or more is definitely abnormal in 97 per cent of cases.

This investigation was undertaken to study the course of a group of adults who presented cardiac enlargement by the above standards, with no other detectable abnormality. The mortality rate of the group as well as information regarding the clinical course of the survivors was used in an attempt to determine the prognostic significance of this isolated finding in otherwise presumably healthy individuals.

MATERIALS AND METHODS

The cases were taken from the files of the Medical Department of the New York Life Insurance Company. We reviewed chest roentgenograms taken on insurance applicants between 1936 and 1953. A history, physical examination,

From the Medical Department of the New York Life Insurance Company, New York, N. Y.
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and urinalysis had also been done in all cases, and in many an electrocardiogram had been recorded. Most of the subjects had been examined at the Home Office Medical Department where chest films are taken in inspiration in the posteroanterior position at a target distance of six feet with an exposure of 1/20 second. We selected those films which showed enlargement of the transverse cardiac diameter utilizing the standards of Ungerleider and Clark.[4] In this study, however, we designated plus 13 per cent as the minimal deviation for enlargement. We discarded those films on which the cardiac border could not be located confidently, as well as those which showed chest deformity, diaphragmatic hernia, or significant pulmonary disease. We eliminated individuals who presented pertinent history or abnormal findings: e.g., history of antecedent hypertension, rheumatic fever, myocarditis or pericarditis, evidence of blood pressure exceeding 150/90 mm. Hg, congestive cardiac failure, valvular heart disease, anemia, chronic respiratory disease, significant chest deformity, metabolic or endocrine disturbance. Finally, we eliminated those with abnormal electrocardiograms. The presence of a normal electrocardiogram does not militate against the diagnosis of cardiac enlargement diagnosed radiologically, since there are many such cases in which the record shows no alterations.[7] Conversely, characteristic changes in the electrocardiogram are frequent in left ventricular hypertrophy, but the patterns are essentially nonspecific and differentiation between primary and secondary T-wave changes often cannot be made with assurance. For this reason we felt that the material would be more homogeneous if such cases were excluded.

There remained seventy cases designated as isolated cardiac enlargement. Electrocardiograms were available in sixty-one of them. This group forms the basis for the study. Because of the nature of the material we cannot determine the exact incidence of this finding. However, it must be small, considering the large number of films reviewed. Of the seventy individuals, sixty-nine were males. The sex incidence has no significance in view of the overwhelming majority of male applicants for life insurance. The age distribution is shown in Table I. The average age of the group was 45½ years. The youngest person was 22 years and the oldest was 65 years. Individuals beyond 65 years were not acceptable candidates for insurance at the time. The cases were followed for one to eighteen years, as shown in Table II. The average was 7.7 years. The procedure of tracing these individuals was begun in 1953 and completed in 1954. All cases were followed successfully, some by direct

TABLE I. AGE DISTRIBUTION AT TIME OF EXAMINATION

AGE GROUP (YEARS)	NUMBER OF CASES
20–29	8
30–39	12
40–49	30
50–59	12
60–65	8

contact and others by indirect methods. The degree of cardiac enlargement ranged from plus 13 per cent, the minimum accepted for this study, to plus 24 per cent. The cardiac silhouettes suggested left ventricular prominence in many cases. Aside from this, their configurations were not unusual. Fluoroscopic examination had not been done. Unfortunately, re-examinations could not be made.

TABLE II. FOLLOW-UP PERIODS

YEARS FOLLOWED	NUMBER OF CASES
18	1
16	1
13	2
12	8
11	7
10	8
9	4
8	4
7	6
6	7
5	8
4	2
3	7
2	3
1	2

TABLE III. DEGREE OF CARDIAC ENLARGEMENT

DEVIATION (UNGERLEIDER-CLARK) (%)	NUMBER OF CASES
+13	4
+14	10
+15	13
+16	21
+17	11
+18	3
+19	3
+20	4
+24	1

RESULTS AND DISCUSSION

There were five deaths in the group. Necropsy was not performed in any of these cases. The lengths of survival and causes of death are listed in Table IV. These data were subjected to statistical analysis. Although the number of cases is too small to yield an entirely reliable conclusion, the analysis shows little or no extra mortality as compared with standard medical experience in a comparable group of individuals. In order to evaluate further this apparent benignity, information relative to the clinical course of the sixty-five survivors was sought. Such data could not be obtained from all individuals because of

difficulties in making direct contacts. However, in forty-two cases, either the individual or a member of his immediate family stated that, aside from minor illnesses, good health had been maintained.

TABLE IV. DEATHS

AGE WHEN EXAMINED	DEGREE OF ENLARGEMENT (%)	AGE AT DEATH	CAUSE OF DEATH
48	+15	60	Coronary thrombosis
49	+16	58	Heart disease
40	+16	43	Carcinoma stomach?
48	+17	59	Coronary thrombosis
57	+18	59	Carcinoma lung

It is difficult to explain this favorable course. One may properly raise the question as to whether these hearts were truly enlarged. Since the determining method is a clinical one, and no pathologic data are available, this question cannot be definitively resolved. All investigators employing this method of cardiac mensuration caution about its limitations. For example, Ungerleider and Clark[4] state that judgment should be used since it is very certain that some hearts whose diameters are above 10 per cent of the expected are normal, just as others in which the heart diameter is distinctly less than the 10 per cent figure allowed, are actually hypertrophied. Although there is general agreement that the method is not infallible, it has been stressed that most of the difficulties and errors are prone to occur in the borderline or slightly enlarged hearts, perhaps up to plus 15 per cent.[5,6,8] Since the transverse cardiac diameters in our cases range from plus 13 to plus 24 per cent, and since forty-three of the seventy cases fall into the categories of plus 16 per cent and over, it is very probable that we are dealing with cardiac enlargement.

In the vast majority of cases of cardiac enlargement, the mechanism is apparent. However, the literature contains numerous reports relative to idiopathic hypertrophy. Cases of cardiac deaths are cited[9-12] in which the outstanding finding was hypertrophy and dilatation of the heart, with no demonstrable etiologic factor either clinically or by necropsy. Others[13,14] have reported deaths, particularly in infants and children, occasionally in adults, in whom pathologic examination revealed endocardial fibroelastosis. Most of these individuals developed cardiac symptoms and died at a relatively young age. It appears highly improbable that our group of cases could represent even some milder, latent form of these serious disease pictures. Similarly, the favorable progress of our cases would serve to exclude coronary disease, which has been a disputed etiologic factor in the production of hypertrophy.[15]

Wilce,[1] Beckner and Winsor[2] and others have pointed out that cardiac enlargement is a frequent isolated finding in athletes who have engaged in excessively strenuous sports over a period of some years. Wilce's material con-

sisted of individuals engaged in various types of athletic competition, and the others observed marathon runners exclusively. They stress the benignity of this finding in these individuals. With this in mind, we reinvestigated most of the members of our group and found that they had never engaged in physically strenuous types of occupation, nor were they former athletes in the sense described by these investigators.

Gore and Saphir,[16] in a study of pathologic material, found evidence of myocarditis in a surprising number of individuals of all ages, in whom clinically, myocardial involvement had not even been suspected. A wide variety of diseases and conditions was found associated with the myocarditides in this series. Aside from rheumatic and diphtheritic carditis, these included specific virus, rickettsial, spirochetal, and fungous diseases, less specific infectious processes, toxic conditions produced by physical or chemical agents, and various metabolic states. In some cases, the myocarditis was isolated and unassociated with any known illness. Autopsy findings included significant enlargement of the heart in many cases. In the light of this pathologic study, it is certainly possible that our group of cases may represent residual cardiac enlargement due to myocarditis resulting from some long forgotten or unimpressive illness, with excellent functional recovery.

In conclusion, it should be more widely recognized that isolated cardiac enlargement may be encountered in apparently healthy adults who have no progressive cardiac disease and in whom an unfavorable prognosis is not warranted.

SUMMARY

A group of seventy asymptomatic adults presenting cardiac enlargement by roentgenogram was studied.

These individuals had no other detectable abnormality and related no significant past history.

The cases were followed for one to eighteen years in an attempt to determine the prognostic significance of this isolated finding in otherwise presumably healthy individuals.

There were only five deaths in the group. The causes of the deaths and lengths of survival are tabulated. Necropsy was not performed in any of these cases.

Statistical analysis of the data shows this mortality to be not in excess of that anticipated for the age groups. The benignity is further evidenced by an uncomplicated course in a significant number of the survivors.

The cause of this apparently benign cardiac enlargement is undetermined.

The role of possible etiologic factors is discussed.

SUMMARIO IN INTERLINGUA

Esseva studiate un gruppo de 70 adultos asymptomatic in qui le roentgenogramma esseva indicative de isolate allargamento cardiac. Iste individuos presentava nulle historia significative. Le grado del allargamento variava

inter +13 e +24 pro cento secundo le standards de Ungerleider e Clark. Le casos esseva tenite sub surveliantia durante periodos de inter 1 e 18 annos. Le mortalitate intra le gruppo e etiam le accumulate datos in re le curso clinic del superviventes esseva utilisate in un effortio a determinar le signification prognostic del isolate allargamento cardiac in iste individuos de alteremente bon apparentia de sanitate. Le datos pertinente relative a 5 mortes esseva tabulate. Le analyse statistic non demonstra un excessive mortalitate in le serie integre. Le benignitate del allargamento cardiac in iste casos es etiam indicate per le absentia de complicationes in le curso de un considerabile numero del superviventes. Le causa de iste allargamento cardiac de character apparentemente benigne remane non-determinate. In nostre discussion de possible factores etiologic nos conclude que le explication le plus plausibile es le antecedentia de un episodio occulte de myocarditis.

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THE DYNAMICS OF THE EISENMENGER COMPLEX. II.

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THE Eisenmenger complex as a pathologic entity was virtually unknown to clinicians until Taussig[1] drew attention to the fact that an ante-mortem diagnosis could be made. The physiologic derangements associated with this condition were shown to consist of (a) increased pulmonary vascular resistance, i.e., the elevated pressure in the pulmonary artery and right ventricle approximating that in the systemic circuit, and (b) evidence of a bidirectional shunt through the interventricular septal defect.[2] Our previous findings[3] excluded a pulmonary factor as the basis for the cyanosis observed in this anomaly. Although the diagnosis is being made with increasing frequency at necropsy, this condition continues to remain a rarity.[4,5] For this reason, the present tendency is to view the Eisenmenger complex as a functional rather than as an anatomic entity.[6]

Since our initial observations of this anomaly in 1951,[3] twenty additional cases have been studied by us at Michael Reese Hospital. Analysis of the clinical, radiographic, electrocardiographic, and hemodynamic data of these cases, and comparison with such information from cases of simple interventricular defects, interventricular defects with pulmonary hypertension, pulmonic stenoses, and a wide variety of other congenital lesions has brought us to a definitive point of view with respect to the Eisenmenger complex. This is summarized in this report.

CASE MATERIAL

Twenty cases of the Eisenmenger syndrome form the basis of this report. Cases 1 to 16 inclusive represent instances of the Eisenmenger syndrome with systemic arterial desaturation. The remaining four cases (17 to 20 inclusive) are instances of the Eisenmenger syndrome with normal systemic arterial saturation. In this laboratory, the borderline of normal systemic arterial saturation is set at 93.0 per cent. All figures above this are assumed to represent normal saturation, and those below this are assumed to represent some degree of desaturation. This is an arbitrary decision. For example, Case 4 had normal

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TABLE I. EISENMENGER COMPLEX—CLINICAL FINDINGS IN THE TWENTY CASES

CASE AGE SEX	DIAGNOSIS OF HEART DISEASE	CYANOSIS	CLUBBING	DYSPNEA	PRECORDIAL BULGE	TRILL	MURMUR SYSTOLIC	MURMUR DIASTOLIC	P_2	HISTORY OF FREQUENT COLDS AND PNEUMONIA
(1)* 19 F	At birth	At age 17 after pneumonia; now lips and nail beds marked	No	Moderate on exertion	No	Systolic, 3rd and 4th, L.I.C.S. parasternally	3rd and 4th L.I.C.S. parasternal line	No	Loud and palpable $P_2 > A_2$	No
(2) 6 M	At birth	From birth; more on exertion; none now	No	Moderate on exertion	No	Diastolic, 3rd. L.I.C.S. parasternally	Short along left sternal border	Long loud, 2nd. L.I.C.S. parasternally	Loud $P_2 > A_2$	Pneumonia once; age 2½ years
(3) 8 M	At age 6	On exertion and exposure to cold; none normally	No	Moderate on exertion	Slight bilateral	No	Grade I to II, mesocardiac	No	Loud $P_2 > A_2$	Frequent colds; pneumonia at age 3 years
(4) 7 M	At age 7	Slight of lips and nail beds	Suggestion	Moderate on exertion	No	No	N.	No	Loud $P_2 > A_2$	Pneumonia at age 16 years
(5) 5 F	At age 1½	At age 1½ with pneumonia, none since	No	No	Left anterior	Systolic, 3rd L.I.C.S. parasternally	Harsh grade IV. 3rd and 4th L.I.C.S. parasternally	No	Loud and palpable $P_2 > A_2$	Pneumonia—four bouts
(6) 3 F	At age 2	No	No	No	No	Systolic pulmonic focus	Harsh grade IV. 3rd and 4th L.I.C.S. parasternally	No	Loud $P_2 > A_2$	No
(7) 15 F	At birth	From birth? Slight of lips and nail beds	No	Moderate on exertion	Left anterior	Systolic at apex	Grade I to II at apex → axilla Grade I to II at base → clavicle	Grade II to III; pulmonic area down to apex	Loud $P_2 > A_2$	No

(8)† 5 F	At birth	From birth; none now	No	Moderate on exertion	Bilateral	No	Grade II to III, 3d L.I.C.S. parasternally	No	Loud $P_2 > A_2$	Two hospitalizations for acute bronchitis
(9) 23 F	At age 16	From age 16, marked now	Marked	Moderate on exertion	No	No	Grade II at 3rd and 4th L.I.C.S. parasternal	No	Loud $P_2 > A_2$	No
(10) 6 M	At age 3	No	No	No	No	Systolic, 3rd L.I.C.S. parasternal line	Grade III loud, harsh 3rd L.I.C.S. and parasternal line	No	$P_2 > A_2$	Pneumonia—four bouts
(11) 3 M	At birth	From birth, present on crying and exertion	No	Considerable on exertion	Slight	Systolic, 2nd and 3rd L.I.C.S.	Grade IV, 3rd L.I.C.S. and parasternal line	No	$P_2 > A_2$ not split	Frequent colds and urination, no pneumonia
(12) 4 M	At age 6 weeks	6 weeks	Slight	Minimal on exertion	Left anterior	No	Grade I to II at apex	No	$P_2 > A_2$	No
(13) 2 F	At age 3 months	At age 2 yr. with heart failure, no cyanosis since	No	Moderate on exertion	Left anterior	Systolic at Erb's point	Grade IV harsh at Erb's point	No	$P_2 > A_2$	Pneumonia at age 7 months
(14) 3 M	At birth	At birth and up to age 2 months, not cyanotic since	No	Slight	Slight left precordial	Systolic over sternum and left parasternal line	Systolic, Grade III over Erb's point	No	$P_2 > A_2$	No
(15) 7 F	At age 7	No	No	No	No	Systolic 2nd and 3rd L.I.C.S. to right and left of sternum	Grade IV, best at 2nd and 3rd L.I.C.S.	No	$P_2 > A_2$	No
(16) 5 M	At birth	Yes	Yes	Yes‡ (constant)	Yes; marked precordial more to the left	No	Grade II, soft, 3rd and 4th L.I.C.S. parasternally	Blowing decrescendo, Grade I, pulmonic area	$P_2 > A_2$	Frequent colds

TABLE I. EISENMENGER COMPLEX—CLINICAL FINDINGS IN THE TWENTY CASES (CONTINUED)

CASE AGE SEX	DIAGNOSIS OF HEART DISEASE	CYANOSIS	CLUBBING	DYSPNEA	PRECORDIAL BULGE	THRILL	MURMUR SYSTOLIC	MURMUR DIASTOLIC	P_2	HISTORY OF FREQUENT COLDS AND PNEUMONIA
(17) 7 M	At age 7 years	No	No	No	No	Systolic 2nd and 3rd L.I.C.S. to right and left of sternum	Grade IV best at 2nd and 3rd L.I.C.S.	No	Loud $P_2 > A_2$	No
(18) 4 M	At age 1 year	No	No	Moderate on exertion	Yes, from birth	Systolic at Erb's point	Grade IV, loud, best at Erb's point	No	Loud $P_2 > A_2$	Frequent, 9 admissions for bronchitis; 1 for pneumonia
(19) 30 F	At age 7 months	No	No	Minimal on exertion	No	No	Grade IV harsh long left sternal border	Blowing decrescendo along left sternal border	$P_2 > A_2$	Pneumonia as an infant
(20) 1 M	At age 5 months	No	No	No	Yes; marked left precordial	No	Grade II to III blowing at 3rd and 4th L.I.C.S. at parasternal line	No	$P_2 = A_2$	2 admissions for pneumonia§

*Case published previously.
†In heart failure at age 2½ years and again one year later; on digitalis since.
‡In heart failure at the time of cardiac catheterization.
§Went into heart failure at the time of second admission; on digitalis since.

saturation when crying and an abnormal saturation at rest. Consequently, we have decided to call all cases instances of the Eisenmenger syndrome and to qualify them by adding "with normal saturation" or "with arterial desaturation." There were sixteen of the latter and four of the former. Eleven were males (ranging in age from 1 to 8 years), and nine females (ranging in age from 2 to 30 years).

CLINICAL FINDINGS

Group 1: Eisenmenger Complex With Arterial Desaturation.—Only three of the sixteen cases with arterial desaturation never showed evidence of cyanosis. In the remaining, cyanosis was present constantly or intermittently. It was never marked, with one exception—Case 16. Contrary to the commonly held view, the cyanosis appeared early, either at birth or in the first two years of life. The two exceptions were the two oldest patients in this group, both females (ages 19 and 23), in whom cyanosis first appeared at ages 17 and 16, respectively. Clubbing was marked in only one case; in three others there was a suggestion of it. Moderate dyspnea on exertion was the rule, but it must be pointed out that in children it is somewhat difficult to evaluate this complaint. One patient (Case 16) had heart failure at the time of cardiac catheterization. Two others had such a history. A precordial bulge was present in twelve of the cases. A thrill, usually systolic, could be felt in the precordial region in all cases. One case had a diastolic thrill. The murmurs were predominantly systolic in time, usually harsh, mostly Grade III (ranging from Grades I to IV) and usually located either at Erb's point or around the 3rd and 4th left intercostal spaces parasternally. Diastolic murmurs were heard in three cases, but there was no evidence of dynamically significant aortic or pulmonic regurgitation in the pressure curves.

The second pulmonic sound was loud in every instance. A history of repeated, upper respiratory infections and/or pneumonia was present in nine of these cases.

Group 2: Eisenmenger Complex With Normal Arterial Saturation.—Three of the four cases were males (ranging in age from 1 to 7 years), and the fourth was a 30-year-old female. Cyanosis and clubbing were absent in this group, but minimal to moderate dyspnea on exertion was present in two of them. The acoustic findings were similar to those described for patients in Group 1. Here, too, upper respiratory infections and/or pneumonia were frequent (three out of the four cases).

ELECTROCARDIOGRAM

The electrocardiograms in all twenty cases showed fundamental sinus rhythm (or tachycardia). Not a single instance of A-V block was found. P-wave abnormalities were seen in five instances. The "electrical" position varied from horizontal to vertical, with all intermediate positions represented. The finding common to all cases was that of right-heart strain, usually isolated (the so-called adaptation type of Donzelot and associates[7]) but sometimes associated with a right-sided conduction defect (incomplete right bundle branch system block) and, in one instance, with left-heart strain. The large diphasic QRS complexes[8] were found in only six of the twenty cases.

FLUOROSCOPIC AND ROENTGENOGRAPHIC FINDINGS

The x-ray picture in the posteroanterior view varied markedly among the twenty cases. Though evidence of right ventricular enlargement, large pulmonary arteries, and hypervascularization of the lung fields was found in almost

TABLE II

CASE AGE SEX	ECG	X-RAY	CATHETERIZATION					REMARKS
			PRESSURES (MM. HG)		SATURATION (%)			
			P.A.	SYSTEMIC	SYSTEMIC	CAVAL	P.A.	
(1) 19 F	Sinus rhythm; horizontal position; right heart strain; possible incomplete RBBSB	Moderate RV enlargement; very prominent P.A. segment; huge R.P.A. and L.P.A.; hilar dance; increased hilar markings; hypervascularization of lung fields	110/60	112/80 (B.A.)	77.0	65.2	68.5	(1) The catheter entered a pulmonary vein which drained directly into the right auricle. This case was published previously.[3] Angiocardiography showed early filling of the aorta.
(2) 6 M	Sinus rhythm; horizontal position; Katz-Wachtel; right-heart strain; incomplete RBBSB	Moderate R.V. enlargement; prominent P.A. segment; hilar dance; increased hilar markings; hypervascularization of lung fields	109/75 to 112/78	102/66 to 107/62 (aorta) 110/73 F.A.	66.7	51.1	65.5	(2) The catheter entered the aorta several times from the right ventricle.
(3) 8 M	Sinus rhythm; semivertical position; right-heart strain; incomplete RBBSB; congenital heart disease	Moderate heart enlargement (R.V.? L.V.?) prominent P.A. segment; hilar dance; increased hilar markings; no hypervascularization of lung fields	95/55	110/60 (B.A. cuff)	84.1	54.2	71.5	(3) Aorta not entered.
(4) 7 M	Sinus rhythm; semihorizontal position; right-heart strain; incomplete RBBSB	Moderate R.V. enlargement; very prominent P.A. segment; hilar dance present; increased hilar markings; no hypervascularization of lung fields	100/60	96/50 (aorta) 116/60 (F.A.)	97.0 (crying) 88.0 (resting)	49.2	61.7	(4) The catheter entered a pulmonary vein which drained directly into the right auricle. Angiocardiography showed early filling of the aorta.

(5) 5 F	Sinus rhythm; indeterminate position; Katz-Wachtel; right-heart strain; incomplete RBBSB; congenital heart disease	Marked R.V. enlargement; moderate L.V. enlargement; prominent P.A. segment; hilar dance; increased hilar markings; hypervascularization of lung fields	89/45	103/65 (F.A.)	86.6	73.2	87.8	(5) Simultaneous right ventricular and femoral arterial pressures were, respectively, 71/2 and 102/65 mm. Hg. Aorta not entered.
(6) 3 F	Sinus tachycardia; semivertica position; Katz-Wachtel; right-heart strain; incomplete RBBSB; congenital heart disease	Marked R.V. enlargement; moderate L.V. enlargement; prominent P.A. segment; no hilar dance; increased hilar markings; hypervascularization of lung fields	65/44	97/66	88.9	66.6	75.8	(6) Aorta not entered.
(7) 15 F	Sinus rhythm; semivertical position; right-heart strain	Moderate R.V. enlargement; slight L.V. enlargement; prominent P.A. segment; no hilar dance; increased hilar markings; hypervascularization of lung fields	143/89	130/71 (innominate) 116/64 (B.A.)	85.9 (rest) 75.4 (exercise)	64.3	71.7	(7) The catheter entered the aorta directly from the right ventricle.
(8) 5 F	Sinus tachycardia; indeterminate position; P-congenitale; rigid heart strain; incomplete RBBSB; digitalis effect; congenital heart disease	Marked R.V. enlargement; marked L.V. enlargement; prominent P.A. segment; no hilar dance; increased hilar markings; hypervascularization of lung fields	85/58	—	80.5	59.3	74.6	(8) Aorta not entered.
(9) 23 F	Sinus arrhythmia; horizontal position; P-congenitale; right heart strain; incomplete RBBSB	Moderate R.V. enlargement; prominent P.A. segment; hilar dance; increased hilar markings; hypervascularization of lung fields	85/60	83/60	57.5	40.1	41.8	(9) The catheter entered the aorta directly from the right ventricle.
(10) 6 M	Sinus rhythm; right heart strain; indeterminate position; incomplete RBBSB	Small heart; no chamber enlargement; prominent P.A. segment; increased hilar markings; hilar dance present	65/10*	100/50 (B.A. cuff)	88.5	48.5	86.7	(10) Aorta not entered.

TABLE II (CONTINUED)

CASE AGE SEX	ECG	X-RAY	CATHETERIZATION					REMARKS
			PRESSURES (MM. HG)		SATURATION (%)			
			P.A.	SYSTEMIC	SYSTEMIC	CAVAL	P.A.	
(11) 3 M	Sinus tachycardia; indeterminate position; Katz-Wachtel; right heart strain; incomplete RBBSB; congenital heart disease	Marked R.V. enlargement; transverse heart with concave P.A. segment almost suggestive of "coeur en sabot"; increased hilar markings; hypervascularization of lung fields; the bifurcation of the trachea forms an angle of ± 120° in P.A.view	60/45	65/45 (aorta)	86.0	54.0	69.2	(11) The catheter entered the aorta directly from the right ventricle.
(12) 4 M	Sinus tachycardia; indetermedinate position; P-congenitale; right heart strain; incomplete RBBSB, congenital heart disease	Marked R.V. enlargement; possible moderate L.V. enlargement; prominent P.A. segment; no hilar dance; increased hilar markings; hypervascularization of lung fields	65/40	100/45 (F.A.)	78.8	55.4	82.3	(12) Aorta not entered.
(13) 2 F	Sinus tachycardia; indeterminate position; Katz-Wachtel; combined heart strain; digitalis effect; congenital heart disease	Marked R.V. enlargement; prominent P.A. segment; no hilar dance; increased hilar markings; hypervascularization of lung fields	55/30	100/50	81.0	50.0	71.6	(13) The catheter entered the left auricle through a patent foramen ovale and could then be placed in the left ventricle. Pressures in the right and left ventricles were, respectively, 70/5 and 90/5 mm. Hg and in the femoral artery 90/40.
(14) 3 M	Sinus tachycardia; indeterminate position; suggestive of P-congenitale; right heart strain; incomplete RBBSB	Marked R.V. enlargement; prominent P.A. segment; increased hilar markings; marked hypervascularization of lung fields	80/55	92/60	90.0	76.6	64.6	(14) The aorta was not entered.
(15) 3	Sinus tachycardia; vertical posi-	Marked R.V. enlargement;	75/55	90/50	92.0	53.0	89.0	(15) The catheter was placed

(15) 3 F	Sinus tachycardia; vertical position; right heart strain; incomplete RBBSB; congenital heart disease	Marked R.V. enlargement; moderate L.V. enlargement; prominent P.A. segment; increased hilar markings; increased vascularization of lung fields; enlarged left auricle	75/55	90/50 (cuff)	92.0 F.A.	53.0	89.0	(15) The catheter was placed in the aorta directly from the right ventricle. There was a small but definite gradient in pressure between the pulmonary arterial and right ventricular pressures.
(16) 5 M	Sinus tachycardia; indeterminate position; P-congenitale; right heart strain; RBBSB	Marked R.V. enlargement; prominent P.A. segment; increased vascularization of the lung fields	70/22	80/60 (F. A.)	35.2†	24.9	27.0	(16) The aorta was not entered.
(17) 7 M	Sinus tachycardia; indeterminate position; right heart strain; possible incomplete RBBSB	Moderate R.V. enlargement; marked L.V. enlargement; prominent P.A. segment; no hilar dance; increased hilar markings; hypervascularization of lung fields	57/37	99/72 (innominate) 86/55 (B.A.)	96.6	72.9	88.5	(17) The catheter entered the left auricle through a patent foramen ovale. The catheter also passed directly from the right ventricle into the left ventricle; the pressures were, respectively, 70/0 and 85/0 mm. Hg and in the femoral artery 110/75.
(18) 4 M	Sinus rhythm; vertical position; right-heart strain	Moderate R.V. and L.V. enlargement; prominent P.A. segment; increased hilar markings; increased vascularization of lung fields	85/40	115/65 (F.A.)	95.0	65.2	92.1	(18) The catheter entered the left auricle through a patent foramen ovale. The aorta was not entered.
(19) 31 F	Sinus tachycardia; semivertical position; right-heart strain	Moderate R.V. enlargement; tremendous, almost aneurysmal, enlargement of main trunks of the P.A. which pulsate vigorously; increased vascularization of lung fields; moderate (2+) enlargement of L.A.	75/45	80/0 L.V.	93.5	72.6	89.3	(19) The aorta was not entered.
(20) 1 M	Sinus tachycardia; indeterminate position; right-heart strain; congenital heart disease	Marked R.V. enlargement; prominent P.A. segment with pedicle; increased hilar markings; increased vascularization of lung fields	75/35	78/45 (F.A.)	93.0	57.3	85.3	(20) The aorta was not entered.

*Diastolic pressure of 10 mm. Hg possibly an artifact
†Patient in heart failure

every case, there was no single "pattern" which could be considered characteristic of the Eisenmenger syndrome in this series. This is an accordance with the findings of Metianu and Durand.[9] A hilar dance was an infrequent finding. The heart size varied considerably, from normal to markedly enlarged. All shapes were seen—globular, "sabot-like" with apparent elongation of the outflow tract of the left ventricle, transverse, and normal.

CATHETERIZATION FINDINGS

A summary of the cardiac catheterization findings is presented in Table II. Only the salient findings are listed. Pressures were registered with a Sanborn electromanometer. The pressures given are approximate values, since the systolic values sometimes vary in the same subject by as much as 10 to 15 mm. Hg, depending on the time when they are registered.

Oxygen content and capacity of the blood samples were determined according to the technique of Van Slyke and Neill;[10] ear and cuvette oximetry, according to the technique of Wood and associates.[11-15] Angiocardiograms were obtained in several patients, but for the sake of brevity they have been omitted. As can be seen in Table II, the aorta was catheterized directly from the right ventricle in five instances. The left ventricle was entered directly from the right ventricle in one case, and the left atrium directly from the right atrium in three instances. In the latter, the diagnosis of patent foramen ovale was made because there was no evidence of any left-to-right shunt at the level of the atria. In two patients a pulmonary vein draining directly into the right atrium was catheterized.

An interesting finding was the existence of a small but definite systolic pressure gradient between the right ventricle and the pulmonary artery in two cases. In Case 13, the right ventricular pressure was 75 to 80/0 mm. Hg, and the pulmonary artery pressure, 55/30, a systolic gradient of about 20 to 25 mm. In Case 15, the right ventricular pressure was 75 to 85/5 mm. Hg, and the pulmonary artery pressure 55/30, a systolic gradient of about 20 to 30 mm.

PATHOLOGIC PHYSIOLOGY

A variety of interpretations of the underlying physiology of the Eisenmenger syndrome have been proposed.[5,6] We agree with Selzer and Laqueur[5] that no strict division should be made between large interventricular septal defects and the Eisenmenger syndrome. The differentiating of the Eisenmenger syndrome rests primarily on the presence or absence of systemic arterial desaturation. However, an explanation of the hemodynamics on the basis of a "double outlet ventricle," while appealing in terms of simple hydraulic principles, is an oversimplification of the complex situation present.

The term "double outlet ventricle" designates a ventricle which propels blood through two outlets with different resistances. In a simple hydraulic model, the volume of flow distributed to each outlet is inversely proportional to the degree of resistance of the individual circuits. Where the differences in resistances are great, all of the output is delivered to the low-resistance circuit.

By analogy, these principles have been employed to explain the hemodynamics of the Eisenmenger syndrome and the necessity for pulmonary hypertension in this condition to maintain an adequate systemic flow.[16,17] However, the validity of such an explanation is supported neither by clinical nor experimental fact. For example, mitral insufficiency is an extreme example of the so-called double outlet ventricle. It has long been asked why with a marked mitral insufficiency, is not all of the left ventricular output expelled through the incompetent mitral valve? How is left ventricular pressure ever elevated sufficiently, under these circumstances, to open the aortic valve? These questions have been partially answered by the experimental studies of Schwartz,[19] and Wiggers and Feil.[20] The latter showed that when no cusps exist, little regurgitation occurs during isometric contraction as long as the intraventricular pressure rise is brusque, and that a priority of ejection is maintained through the aortic valve. When the vigor of ventricular contraction, for any reason, is weakened and, as a result, pressure within the chamber rises gradually, marked regurgitation occurs through the mitral valve and circulatory failure develops. Some of the factors, as they apply to a model, have been reported from this laboratory.[23] Similar phenomena have been demonstrated in tricuspid insufficiency.[21]

More closely related to the problem of the Eisenmenger syndrome are the studies by Hawley and associates[22] on the hemodynamics of experimental interventricular septal defects. Under these circumstances it was shown that blood is ejected through the aortic valve earlier than through the septal defect. This condition prevailed even when as much as one-half the stroke output of the left ventricle passed through the shunt. The basis for such priority of ejection here, as in mitral and tricuspid insufficiency, is, at present, not wholly clarified. This is being studied in a model in this laboratory.[31] It is apparent, however, that in all of these conditions, the dynamic state of the ventricle is of more importance than just the simple pressure relationship in the two ventricular outlets.

Thus it can be seen that, except in those few instances of the Eisenmenger syndrome in which the aorta is completely dextraposed, the concept of the double outlet ventricle will not suffice to explain the situation actually found clinically or experimentally.

If it is accepted that other dynamic factors are primary determinants of the hemodynamics of the Eisenmenger syndrome, it follows that there is no need to insist that the pulmonary hypertension, which characterizes the entity, is the necessary feature permitting the systemic circulation to receive an adequate portion of the total cardiac output. It has, in fact, long been our conclusion from a study of our own material and that reported in the literature, that the pulmonary hypertension in the Eisenmenger syndrome is an entirely fortuitous occurrence and has none of the teleologic significance attributed to it by Edwards and by others.[24,25] There are a number of facts which support such a viewpoint. It has not been possible in this department, or elsewhere, to show any consistent linear relationship between pulmonary flow on the one hand, and pulmonary pressure on the other. This is true regardless of whether increased

pulmonary flow is due to a left-to-right shunt from an interatrial septal defect, an interventricular septal defect, or a patent ductus arteriosus. We have, for example, studied two cases of interventricular septal defect with perfectly normal pulmonary pressures in which the cardiac output at rest is practically triple the normal, and the pulmonary flow more than double. The distensibility of the pulmonary circulation is so great that the fear of flooding the pulmonary capillary bed, when the pulmonary artery is subjected to the systemic pressure, is remote. The very rapid flow in such cases itself, by producing turbulence in the communication, dissipates the systemic pressure.

If the pulmonary arteriolar changes seen in Eisenmenger's syndrome develop (or persist) as a compensatory mechanism to maintain an effective systemic flow, then it is reasonable to ask several pertinent questions: (1) Why does pulmonary hypertension fail to develop in the majority of instances of dynamically significant interventricular septal defects? (2) Why is pulmonary hypertension lacking in other anomalies where its presence would serve a real purpose? (3) Why is pulmonary hypertension present in association with some cardiac anomalies where it can serve no useful purpose?

In cases of so-called "malignant" ductus arteriosus, where shunts are enormous and lead to irreversible congestive heart failure and early death, increased pulmonary resistance could, under these circumstances, be lifesaving, and yet it does not occur and vascular changes in the lungs do not appear.

Pathologic changes in the pulmonary arterioles, similar to those found in Eisenmenger's complex, have been described in instances of coarctation of the aorta with patent ductus arteriosus, and these changes have been ascribed to the existence of the aortopulmonary communication.[26] However, such a viewpoint ignores the fact that in 50 per cent of the coarctations that have been studied by catheterization technique, pulmonary hypertension is found in the absence of a coexistent patent ductus.

Further evidence against attributing pulmonary hypertension in congenital heart disease to aortopulmonary communication exists in those unique cases of pulmonary stenosis with intact ventricular septum where pulmonary hypertension is present. We have observed two such cases, one of which has been the subject of a previous report.[27] Other cases of pulmonic stenosis with increased pulmonary pressure have been reported.[28] In these, an interventricular septal defect with left-to-right shunt was also present. It would appear, then, that the evidence would not support the concept that increased pulmonary resistance develops in the Eisenmenger syndrome as a compensatory mechanism to either protect the capillary bed from increased pressure, or to maintain an adequate systemic flow.

In many of our cases of the Eisenmenger syndrome, we have been struck by the extraordinarily high incidence of repeated bronchopulmonary infection. In one case of the Eisenmenger complex, reported by Old and Russell,[29] acute inflammatory changes were found in the intrapulmonary arteries as well as medial hypertrophy and intimal fibrosis. To Soulie and his group,[30] the changes seen would be due to a pulmonary arteritis. These acute changes were not

considered to be related to the Eisenmenger complex by Civin and Edwards,[25] but clarification of this aspect of the subject must await more extensive examination of such material.

The possibility exists that these pulmonary vascular changes are not fundamentally inflammatory in character, but actually represent anomalous development of the entire pulmonary vascular tree. Such an explanation would best account for the occurrence of pulmonary hypertension in association with cardiac anomalies where, as noted above, no teleologic or physiologic function is served, and, on the other hand, for the absence of increased pulmonary resistance where the continuance of life makes such a situation mandatory. At the present time, there is insufficient evidence to permit one to resolve this problem, but from the evidence at hand, the fortuitous nature of increased pulmonary vascular resistance in the Eisenmenger syndrome seems conclusive.

SUMMARY

A series of twenty cases of the Eisenmenger complex, seen over the past few years at this hospital and subjected to catheterization, forms the basis of this study.

A classification is presented and the clinical features analyzed.

The physiology of the Eisenmenger syndrome may be summarized briefly as consisting essentially of the hemodynamics of a large interventricular septal defect wherein the dynamics of muscular contraction are the major determinative factors, and wherein a large number of as yet undefined factors undoubtedly also play a role. An explanation of the pathophysiology of the Eisenmenger syndrome merely on a simple hydraulic principle of two circuits of unequal resistance in parallel is untenable. The increased pulmonary resistance present in this anomaly is of purely fortuitous occurrence. It is most probable that inflammatory changes or a coexistent congenitally anomalous basis are responsible for the anatomic and physiologic derangement of the pulmonary circuit. The rapidity and degree with which these changes develop are the determinants as to whether any given case presents a partial or complete picture of the Eisenmenger syndrome or remains that of uncomplicated interventricular septal defect.

SUMMARIO IN INTERLINGUA

Le base del presente studio es un serie de vinti casos del complexo de Eisenmenger observate durante recente annos al Hospital Michael Reese de Chicago.

Le material es classificate e le datos clinic es analysate.

Le physiologia del syndrome de Eisenmenger consiste in essentia del hemodynamica de un grande defecto del septo interventricular. In illo le dynamica del contractiones muscular es le principal factor determinante, sed illo etiam involve sin dubito un considerabile numero de nondum definite factores. Il non es tenibile explicar le pathophysiologia del syndrome de Eisenmenger simplemente super le base del principios hydraulic de due circuitos in parallela con resistentias inequal. Le augmentate resistentia pulmonar que es presente in iste anomalia es de occurrentia purmente fortuite. Il es multo probabile que

cambiamentos inflammatori o un coexistente e congenite base anormal es responsabile pro le disrangiamento anatomic e physiologic del circuito pulmonar. Le rapiditate e le grado del disveloppamento de iste cambiamentos determina si un certe caso representa le syndrome de Eisenmenger de forma partial o complete o si illo remane un non-complicate defecto del septo interventricular.

We are indebted to the physicians who permitted us to use their cases and to the catheterization team for obtaining the data used.

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THEORETIC CONSIDERATIONS OF THE TIME COURSE OF PRESSURE DEVELOPED AND VOLUME EJECTED BY THE NORMAL AND DILATED LEFT VENTRICLE DURING SYSTOLE

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THE dilated heart is a major problem in clinical cardiology. Although Starling's law of the heart reveals the favorable influence of diastolic filling upon the force of contraction, his studies equally well emphasize the disadvantages of excessive dilatation. Some interesting features of the normal heart as a pumping organ pointed out by Gladstone[1] stimulated other studies[2] which indicated certain mechanical peculiarities of the heart as a pump, particularly mechanical handicaps of the dilated heart.

Because of the importance of the dilated heart in clinical medicine and its refractoriness to treatment, theoretic studies are presented contrasting the pressure developed and the volume of blood ejected by the dilated left ventricle with those of the normal-sized heart. These reveal mechanical handicaps of dilatation. For example, if it is assumed that (1) the left ventricle is spherical, (2) the tension developed by the cardiac muscle fibers is constant throughout systole, (3) the tension is equal to that necessary barely to overcome the diastolic pressure, and (4) the rate of shortening of the fiber is constant; then it is possible to calculate the time course of intraventricular pressure and the volume of blood ejected during systole (Figs. 1 and 2).

The hoop-tension developed by muscle tension or contraction may be defined by the equation:

$$T = \pi r^2 P, \qquad (1)$$

where T = tension or force, in dynes (assumed to be constant),
r = radius of the spherical left ventricle, in cm.,
and P = pressure in mm. Hg (1 mm. Hg pressure is equal to 1333.2 dynes/cm.^{2}).

Thus, from the foregoing assumptions and Equation (1), it becomes evident that pressure varies inversely with the square of the radius, intraventricular pressure rising with ventricular emptying but without any increase in the tension developed by the myocardial fibers during this rise in pressure. Fig. 1 shows

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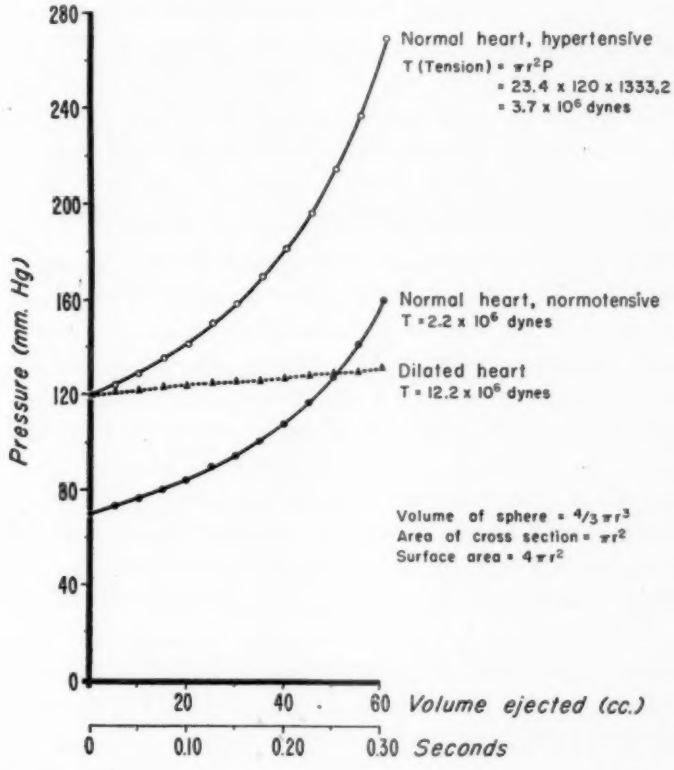

Fig. 1.—Time course of pressure for a normal-sized left ventricle (end-diastolic volume of 85 c.c.) and a dilated one (end-diastolic volume of 500 c.c.), in which the tension of muscle shortening and rate of shortening remain constant throughout the period of systolic ejection of 60 c.c. of blood. The tension developed was considered to be that necessary just to overcome the diastolic aortic pressure existent at zero time on the graph.

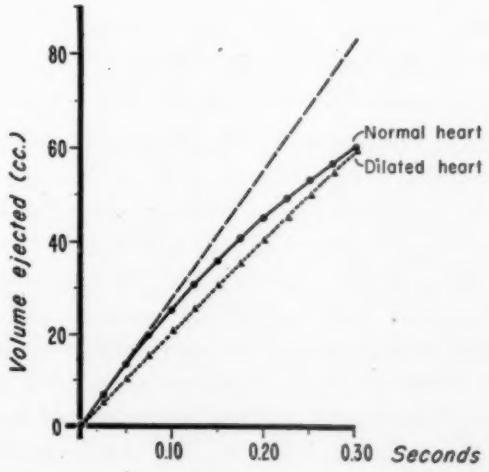

Fig. 2.—The time course of volume ejected by a normal-sized left ventricle (end-diastolic volume of 85 c.c.) and a dilated left ventricle (end-diastolic volume of 500 c.c.), from which 60 c.c. were ejected at a constant rate of muscle fiber shortening. The broken line reveals the time course of the rate of ejection if the initial rate of volume ejection of the normal heart were continued throughout the ejection period.

the time course of the increase in left ventricular pressure from 70 mm. to 160 mm. Hg as it empties from an end-diastolic volume of 85 c.c. to eject 60 c.c. of blood. Obviously, therefore, the heart of normal size could reduce its tension of contraction as systole progresses and still maintain a normal level of blood pressure. If the diastolic blood pressure were 120 mm. Hg, the same normal left ventricle would raise the systolic pressure to 269 mm. Hg without further increasing muscle tension during contraction as it ejected 60 c.c. of blood (Fig. 1).

On the other hand, if a dilated left ventricle with an end-diastolic volume of 500 c.c. were to eject 60 c.c. of blood at a constant rate and the fibers contracted with constant tension, it would raise a diastolic pressure of 120 mm. Hg to a systolic pressure of only 131 mm. Hg, resulting in a low pulse pressure (Fig. 1). This type of mechanical disadvantage may possibly be responsible in part for the elevation in diastolic blood pressure and low pulse pressure observed so frequently clinically in association with cardiac dilatation. To raise the pulse pressure to a higher level in order to insure more adequate circulation, the muscle fibers must contract with increasing tension as systole progresses, a work handicap in comparison with the normal heart. It is possible to visualize or calculate readily the greater tension of muscle contraction that would be necessary if the dilated left ventricle were to maintain an arterial pressure of 269/120 mm. Hg. This increased tension could be of considerable physiologic importance, especially when it is also realized that the muscle fibers of the dilated heart are diseased.

Fig. 2 reveals the variations in the volume-rate of ejection by the left ventricle for the normal sized heart (85 c.c. end-diastolic volume and 60 c.c. stroke volume). It is evident that the volume ejected would be maximal initially and minimal terminally because the volume of a shrinking sphere,

$$V = 4/3\pi r^3,$$

decreases with the cube of the radius. The dilated left ventricle (500 c.c. end-diastolic volume and stroke volume also of 60 c.c.) would have essentially a constant volume-rate of output during systole under similar conditions (Fig. 2).

The normal heart could afford to "loaf" progressively as systole continues, because myocardial tension and volume output can decrease and the heart still maintain a normal blood pressure of 110/70 mm. Hg, for example. The dilated heart, on the other hand, must progressively work harder or equally hard throughout systole because myocardial tension must be increased or maintained and volume of output must be maintained as systole progresses. Thus, despite the assumptions made for convenience of presentation of the ideas, the theoretic considerations of the time course of pressure developed and of volume-rate of ejection by the normal-sized and dilated heart reveal hemodynamic problems that are not solely of academic interest. In addition, such considerations of pressure reveal a possible hemodynamic justification for surgical excisions of a ventricular aneurysm or possibly removal of a segment of a greatly dilated ventricle to improve the mechanical state of the heart as a pumping organ, ideas which require further detailed considerations.

SUMMARIO IN INTERLINGUA

Theoric considerations del "carga" supportate per le normal e per le grandemente dilatate corde servi a demonstrar que le grandemente dilatate corde labora sub conditiones que es considerabilemente disavantagiose in comparation con illos del corde de dimensiones normal. Le differentia es ancora plus evidente in le presentia de hypertension arterial diastolic. Iste considerationes es usualmente negligite proque "labor in le senso physiologic" pote occurrer ben que il ha nulle "labor in le senso physic."

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ISOLATED CONGENITAL DEXTROCARDIA

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IN DEALING with a case of congenital isolated dextrocardia, two problems arise: (1) Are the chambers of the heart inverted? (2) What is the nature of congenital cardiac lesion which is frequently present?

It would be of value if the answers to these questions could be sought by the simpler methods of cardiologic examination.

In Table I only those cases have been included which have satisfied the following criteria: (a) two ventricles were present; (b) the side of the arterial and venous chambers was determined either by autopsy, angiocardiography, or cardiac catherization.

Because of these requirements, only fourteen of the thirty-six autopsy summaries in Lichtman's[1] classic paper have been included in the table. Similarly, only three of the eight cases reported by Donzelot and associates[2] have been included. If we look at the totals at the bottom of the table, we will see that the figures obtained support the widely held belief that in isolated dextrocardia, the chambers of the heart are commonly not inverted.

Next we see that when the arterial ventricle is on the left, the arch of the aorta is also on the left, although there is one exception to this rule. This exception is not surprising because a right aortic arch may persist even in normal hearts. (A similar general correlation may apply in the unusual circumstance when the chambers of the heart are inverted. However, only three such cases appear on the table.) Similarly, we see that there is a close correspondence between the side of the superior vena cava and the venous chambers of the heart. We cannot determine the side of the superior vena cava by simple examination, but we can determine the side of the sinuatrial node by the direction of the P wave in Lead I. The whole of this subject of the side of the superior vena cava, the side of the sinuatrial node, and the side of the venous auricle of the heart has been correlated to the sign of the P wave in Lead I by Campbell and Reynolds,[10] and in a later paper by Campbell and Forgacs.[11] They have shown that in situs inversus, in isolated dextrocardia as also in levocardia, P_1 is erect if the venous auricle is on the right, and P_1 is inverted if the venous auricle is on the left.

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TABLE I

AUTHOR	NO. OF CASES	ARTERIAL CHAMBERS	AORTA	VENOUS CHAMBERS	S. V. C.
Lichtman[1]	13	9 left 3 right 1 uncertain	8 left + 1 right 2 right + 1 left	9 right 3 left	? 2 left + 1?
Steinberg et al.[3]	2	2 left	?	2 right	2 right
Donzelot et al.[2]	3	3 left	3 left	3 right	2 right +1 left
Burchell and Pugh[4]	1	1 left	1 left	1 right	1 right
Etchegaray and Delzar[5]	1	1 left	1 left	1 right	1 right
Hel'mer[6]	1	1 left	1 left	1 right	1 right
Chapman and Gibbons[7]	1	1 left	1 left	1 right	1 right
Aren[8]	1	1 left	1 left	1 right	1 right
Ruskin et al.[9]	1	1 left	1 left	1 right	1 left
Gubbay	1	1 left	1 left	1 right	1 right
TOTAL	25	21 left 3 right	18 left + 2 not stated + 1 right 2 right + 1 left	21 right 3 left	

In summary, if we have a case of dextrocardia and it is isolated, and further if the arch of the aorta is left sided and P_1 is erect, then it is quite clear that the chambers of the heart are not inverted.

CASE REPORTS

CASE 1.—A woman, aged 21, presented for the care of her pregnancy, was referred to me for an opinion about her heart. In brief, she was a healthy young woman with very good exercise tolerance. The dextrocardia heart appeared normal in size, but there was a systolic thrill and bruit present maximal in the third right intercostal space. No cyanosis, no clubbing. Hemoglobin, urine, blood pressure, etc., were normal. She carried her pregnancy normally but was delivered at term by Caesarean section by her attending obstetrician on the grounds of a flat pelvis. At operation, the abdominal viscera were found to be normal and were normally situated.

Figs. 1, 2, and 3 show the posteroanterior (P.A.) and oblique views of the heart. Screening showed that the arch of the aorta was left sided. Note that the oblique views are in accord with the suggestion that a counterclockwise rotation of the heart has carried the mass of the left ventricle forward. Cardiac catheterization showed that the superior vena cava and venous chambers of the heart were right sided.

Fig. 4 shows the limb leads and the unipolar limb leads. Note the erect P wave in Lead I is in accordance with the right superior vena cava as shown by cardiac catheterization. Note the back of the heart pattern, a deep Q, small r, and inverted T in aV_L which is reflected in Lead I. Note the septal pattern with an RS and erect T in aV_R, again an index of the considerable counterclockwise rotation and dextroversion of the heart. Note also the left ventricular pattern in aV_F reflected in Leads II and III.

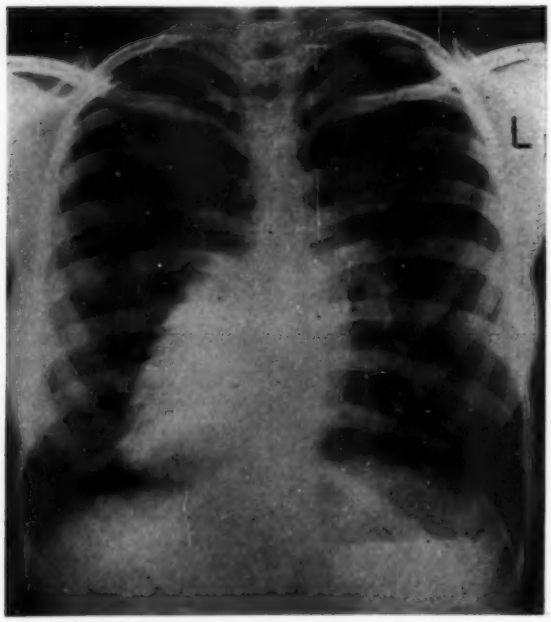
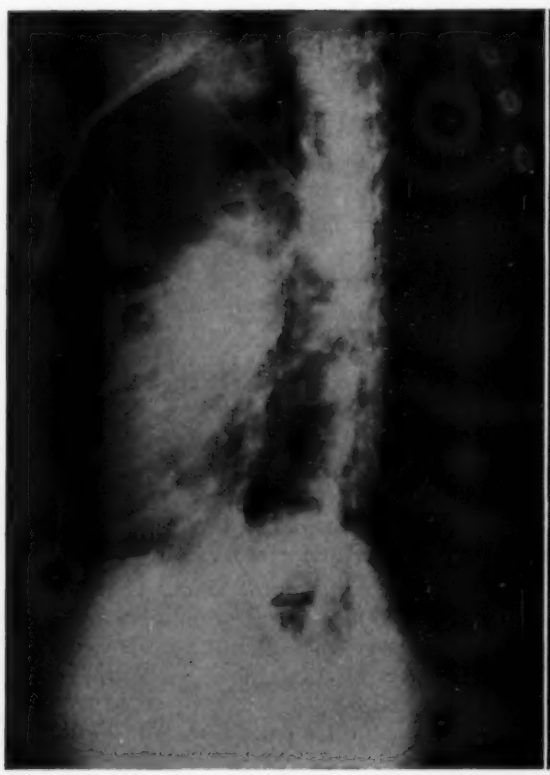


Fig. 1.—Chest film. Posteroanterior view. Case 1.



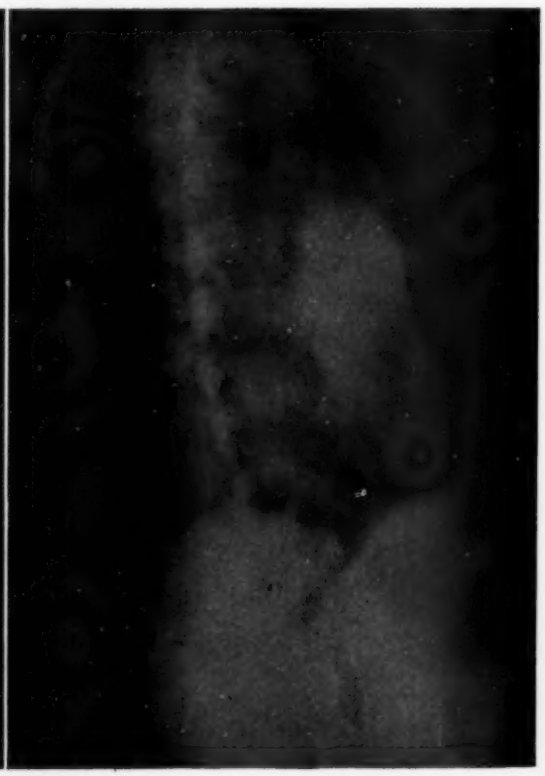


Fig. 2. Fig. 3.

Fig. 2.—Chest film. Left anterior oblique view. Case 1.
Fig. 3.—Chest film. Right anterior oblique view. Case 1.

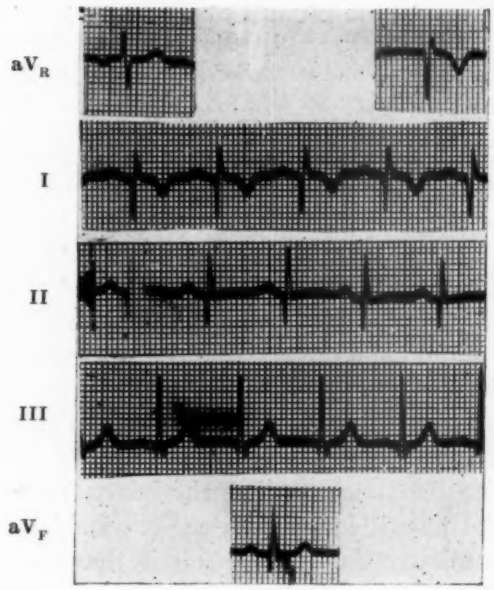


Fig. 4.—Limb leads and unipolar limb leads. Case 1.

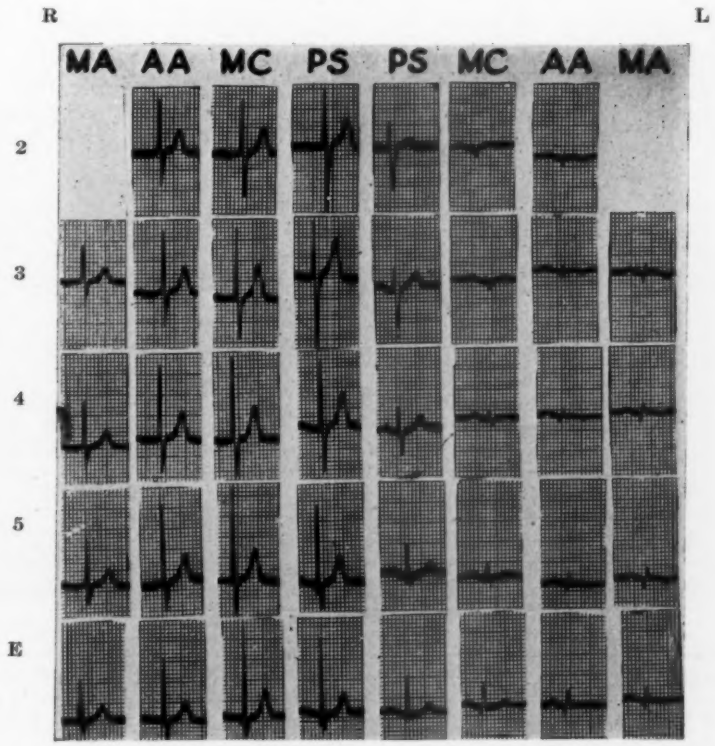


Fig. 5.—See text. Case 1.

Fig. 5 shows an exploration of the front of the chest with a unipolar electrode. The electrode explored the chest horizontally from right to left at the levels of the junction of the rib spaces and the sternum. The horizontal level at the epigastrium (E) was also explored. Note the cavity or back of the heart patterns above and to the left, the septal patterns above and to the right, and the left ventricular patterns below.

It is worthwhile to draw attention to the fact that had the front of the chest simply been explored by V_R leads from left to right, we might have been tempted to accept the erroneous conclusion that the arterial ventricle lay further to the right.

A word should now be said about the general anatomy of these hearts. The venous auricle lies above and to the right, the inflow tract of the venous ventricle passes downward to the right and backward, and the outflow tract then turns upward. The pulmonary artery may pass to the left and across in front of the aorta as in Aren's[8] case, or behind the aorta as in Hellmer's[6] case. It may also pass upward and to the right as it was shown to do by angiocardiography in the case reported by Ruskin and associates.[9]

It is essential to realize that not only has the heart turned to the right on its anteroposterior axis, but also it has undergone a considerable counterclockwise rotation on its longitudinal axis. The result is that the arterial ventricle has come forward to occupy about one-half the anterior surface of the heart. In addition, the isolated dextrocardia heart may lie vertically or its long axis may pass obliquely downward and to the right as in Case 1. The case reported by Chapman and Gibbons[7] shows a vertically placed heart, and they obtained right ventricular ECG patterns to the right, and left ventricular ECG patterns to the left of the heart. Alzamora Castro[12] obtained similar convenient ECG patterns, but he did not publish the radiologic findings in his case. It is tentatively suggested that commonly in the vertical isolated dextrocardia heart the arterial ventricle lies to the right and the venous ventricle to the left. It would

TABLE II

AUTHOR	CASE NO.	aV_R	aV_L	aV_F	LEAD I	LEAD II	LEAD III
Burchell and Pugh[4]	1	rsr't −	qsT −	qRsT +	qsT −	qRsT +	qRsT +
	2	rST +	QrT −	RT +	RT −	RT +	RT +
	3	qst −	rt +	RT +	rt +	RT +	RT +
	4				QRT −	qRT +	qRsT +
Chapman and Gibbons[7]	—	QST −	RT −	qRT +	RT −	RT +	qRsT +
Aren[8]	—				R	qRst +	Rst +
Molari[13]	—				QRt +	qRT +	qRT +
Alzamora Castro[12]	2	rsr'T −	QRT −	RST +	QRt +	qRsT +	RST +
Etchegaray and Delzar[5]	—				RT +	RT +	QSt +
Gubbay	1	RST +	QrT −	qRst +	QrT −	QRT +	qRT +

seem that, commonly in the obliquely placed isolated dextrocardia heart, the arterial ventricle lies mainly below and the venous ventricle above and to the right. The angiocardiogram in case one of Burchell and Pugh[4] and the detailed precordial exploration in our Case 1 support this view.

The second question asked at the introduction to this paper was, "How can we determine the nature of the congenital cardiac lesion present by the simpler methods of cardiologic examination?" It is essential to have a basis of normal before we can proceed with the abnormal. There is very scanty information about the radiologic findings in such hearts that are not grossly diseased. However, in Table II is presented a review of the ECG findings in cases of isolated dextrocardia with functionally normal hearts. Two interesting general trends appear in the patterns recorded. It is common for aV_L to reflect potentials from the back of the heart due to counterclockwise rotation. It is common for aV_F to face the left ventricle. Lead I may reflect the patterns of aV_L, and Leads II and III may reflect the patterns of aV_F. Variations, of course, will occur with varying degrees of dextroversion and of rotation of the heart.

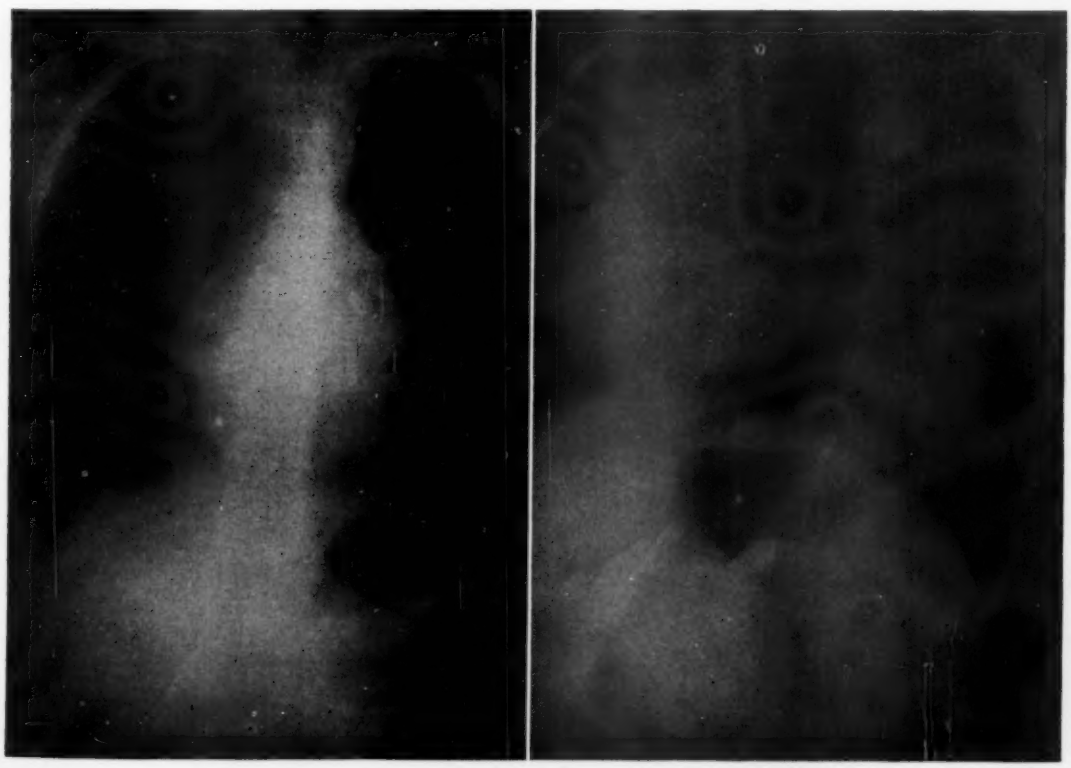


Fig. 6. Fig. 7.

Fig. 6.—Chest film. Posteroanterior view. Case 2.
Fig. 7.—Chest film. Left anterior oblique view. Case 2.

CASE 2. —This case is reported to point up some of the difficulties. A 9-year-old boy was referred for a routine chest x-ray and the picture obtained led to further study and to the opinion that the case was one of isolated dextrocardia. Routine history and physical examination and laboratory tests were negative. Figs. 6 and 7 show the P.A. and left oblique views of the heart

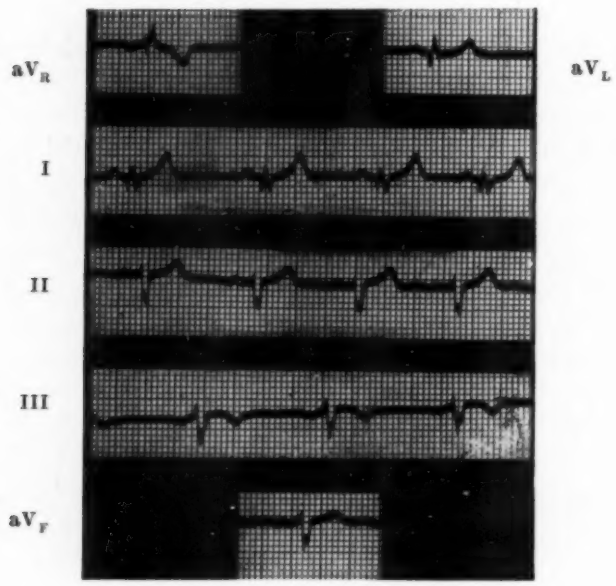


Fig. 8.—Limb leads and unipolar limb leads. Case 2.

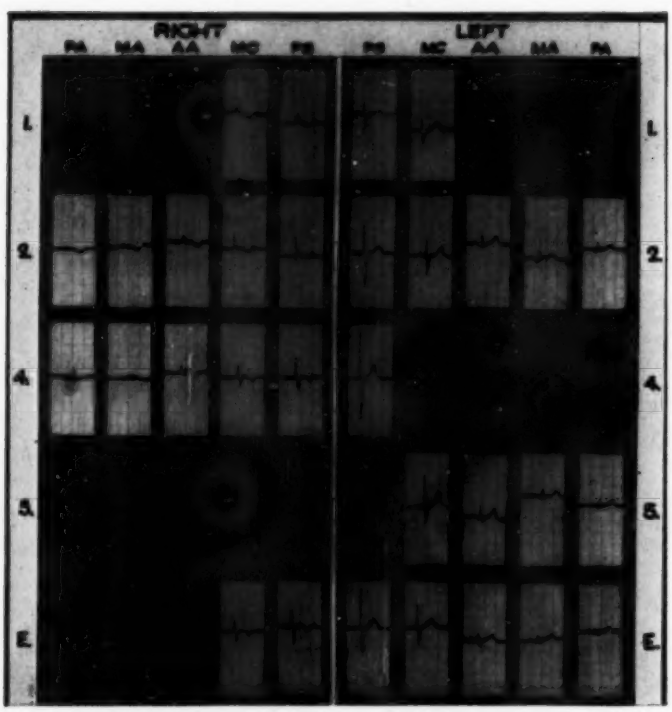


Fig. 9.—See text. Case 2.

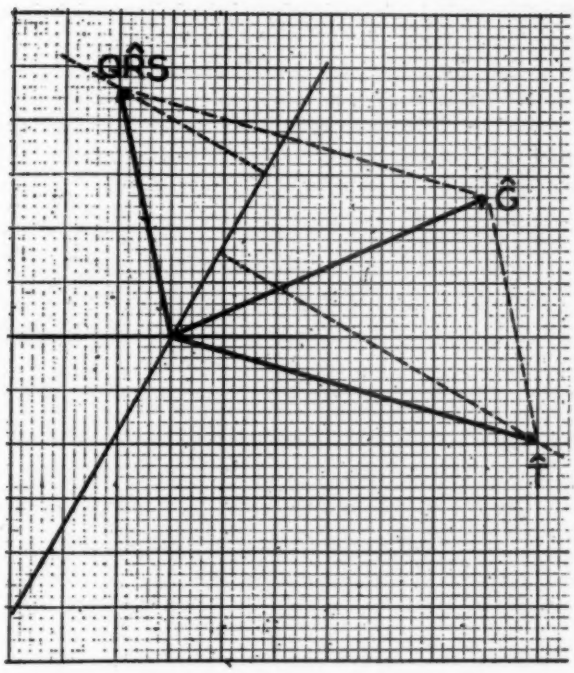


Fig. 10.—$\hat{A}_{QRS}$, $\hat{A}_T$, and $\hat{G}$. Case 2. Net values of QRS and T by the method of Ashman and Byer.[15] $\hat{G}$ measures 8¼ units and forms an angle of 77° with $\hat{A}_{QRS}$.

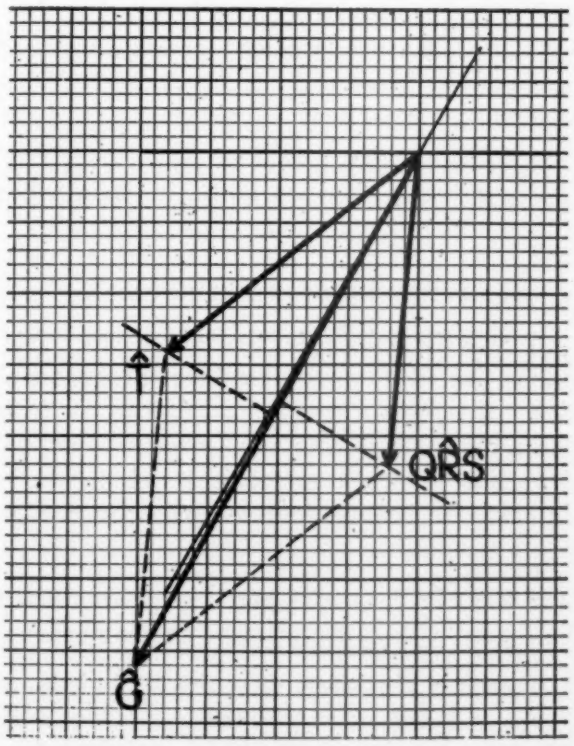


Fig. 11.—$\hat{A}_{QRS}$, $\hat{A}_T$, and $\hat{G}$. Case 1. $\hat{G}$ measures 10¼ units and forms an angle of 24° with $\hat{A}_{QRS}$.

of this boy. Contrast the "normal" backward bulge of the left ventricle in the left oblique view in Case 2 with the flattened posterior aspect of the left oblique view in Case 1. Fig. 8 presents the limb lead and unipolar limb lead ECG patterns in Case 2. These patterns are in contrast to those obtained in Case 1. In particular, note that the pattern in aV_F does not suggest that this lead faces the left ventricle. Fig. 9 represents an incomplete exploration of the front of the chest in Case 2, carried out in the same way as described for Case 1. In spite of this further exploration the over-all ECG picture remains somewhat confusing.

By way of pointing up further the contrast it is worthwhile to consider the projection of the spatial QRS and T vectors on the frontal plane. When this is done by the method of Grant and Estes,[14] it is seen that in Case 1 the QRS and T vectors are directed downward and rightward with the T vector rightward of the QRS. In addition the spatial QRS-T angle would not seem to be unduly wide. In Case 2 the QRS vector is directed upward and slightly rightward, and the T vector is directed leftward a little below the reference level of Lead I. The QRS-T angle is obviously abnormally wide. There may be some irregularity of conduction in the case or it may be that in terms of spatial vectors Case 2 belongs in the S_1, S_2, S_3 pattern discussed by Grant and Estes.[14] $\hat{A}_{QRS}$, $\hat{A}_T$ and $\hat{G}$ for both these cases are presented in Figs. 10 and 11.

SUMMARY

A case of isolated dextrocardia with a functionally normal heart is presented. The method of deciding whether the chambers of the heart are inverted in such cases is described. It must not be concluded that this method will give satisfactory results when applied to cases of isolated dextrocardia with complicated congenital lesions of the heart. A survey of the ECG findings in isolated dextrocardia in functionally normal hearts is given.

A second case appearing to belong to the group of isolated dextrocardia is described. This case is contrasted with the general pattern obtained.

SUMMARIO IN INTERLINGUA

Es presentate un caso de isolate dexterocardia con corde functionalmente normal. Le methodo es describite pro determinar in tal casos si o non le cameras del corde es invertite. Il non es a concluder que iste methodo pote render resultatos satisfactori in casos de isolate dexterocardia con complicate lesiones congenite del corde. Nos presenta un revista del constationes electrocardiographic obtenite in casos de isolate dexterocardia con cordes functionalmente normal.

Es describite un secunde caso que pertine apparentemente al gruppo de isolate dexterocardia. Iste caso es contrastate con le norma general.

Dr. Armstrong, Department of Physiology, University of Manitoba, performed the cardiac catheterization on Case 1. Dr. Arthur Childe kindly drew the author's attention to Case 2 and screened both cases with him. Dr. William Taylor gave permission for the study of Case 2.

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NEW EARLY DIAGNOSTIC SIGN OF PHLEBITIS OF THE LOWER EXTREMITIES

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THE difficulties in the diagnosis of the inflammatory and thrombotic processes of the veins of the lower extremities justify all the investigations directed toward their prompt recognition, in time to diminish the dangers. There have been described almost twenty clinical signs concerning this problem.

Since the signs of disease in the deep veins of the lower extremities, especially in the cases in which embolic accidents are most feared, remain difficult to recognize[1-74] we thought worthy of study the new exploratory test that we are about to propose.

MATERIAL

There were studied fifty-eight patients: thirty-two with phlebitis, six with varicose veins, twelve with arteriosclerosis of the lower extremities, four cases of Buerger's disease, thromboangiitis obliterans, two patients with postphlebitic disturbances, and two with nonspecific venous disturbances.

The first twenty-two patients, that is the ones with presumptive phlebitis of the deep veins, had conditions favoring the appearance of phlebitis (parturition, abdominal surgery, varicose veins, old healed phlebitis) and all had spontaneous pain in the popliteal region, the calf or both. Some had slight fever, tachycardia, slight leukocytosis and high sedimentation rates, some dimunition of the oscillometric readings in the affected leg, and all healed with the usual treatment for phlebitis.

METHOD OF STUDY

With the patient in the recumbent position and the extremity to be explored slightly flexed, a sphygmomanometer mercury cuff was applied above the knee, with a pressure of around 4 cm. Hg; the venous hypertension thus provoked induced in the cases of deep phlebitis, pain in some place, most often in the popliteal region or the calf. This pain increased during 5 minutes, sometimes was equal to the spontaneous pain, and disappeared almost instantaneously after releasing the pressure.

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It was not considered as a positive "sign," when the pain did not appear, or did not increase with the pressure or when the pain did not disappear after releasing it.

This new sign of provoked pain was compared with the usual diagnostic signs of deep phlebitis; the signs of Homans, Bailey, Newman, Castaneda-Uribe or sign of the toe, and the calf's swelling.

RESULTS

In all the thirty-two patients with phlebitis the signs of Homans, Bailey, and Newman, and the "cuff" sign were studied, and the signs of Moses, Castaneda-Uribe and the swelling of the calf in only twenty-two of them. The results were as follows:

	(%)
Positive cuff sign	100
Positive Homans sign	81.2
Positive Bailey sign	43.7
Positive Newman sign	25
Positive Moses sign	68.2
Positive Castaneda-Uribe	27
Positive swelling of the calf	36.3

In the six patients with varicose veins we did not find a single positive sign.

In the twelve patients with arteriosclerosis, four only had some sign of phlebitis: one had a positive sign of Moses and also the cuff sign; another had positive cuff, the Bailey and the Newman signs and two other cases, only positive cuff sign.

The four patients with Buerger's disease gave the following data: two without any positive sign; one with positive cuff and Moses signs; and the fourth case only positive cuff sign. The postphelibitic case had only positive cuff sign.

In the two with nonspecific disturbances, one suffered a slight subcutaneous rupture of unknown mechanism which showed a positive cuff sign; another patient who had a recent occlusion of the cephalic vein, probably caused by an intravenous injection, did not give a positive sign.

DISCUSSION

A clinical sign is considered positive when it precedes with great frequency the complete establishment of all the characteristic symptoms of a pathologic entity; it is also considered a positive sign when it belongs to the clinical picture of a disease fully developed.

In the cases in which a presumptive diagnosis of phlebitis has been made in the first hours or days of the process, a clinician cannot let the disturbance follow its natural course, but he would have to treat it as if the disease certainly existed, or expose the patients to dangerous complications. In the twenty-two patients that we have considered as having incipient phlebitis there could be

few that had some undiagnosed process such as the avitaminosic disturbances described by Eiseman,[17] the traumatic complications analyzed by De la Barreda and Castro[14] or some cases of phlebodynia like those reported by Pearson.[57]

Even though we consider well established the fact that the "cuff" sign was positive in 100 per cent of our cases of phlebitis, especially if it is compared with the 81.2 per cent of positive cases of Homans' sign, we do not think of it as a pathognomonic sign, since our material was not homogeneous and the diagnosis of incipient phlebitis never can be sustained with absolute certainty.

Therefore, the value of the positivity of the "cuff" sign shares the limitations common to all clinical positive signs, revealing the onset of a certain disease even though we have also found the cuff sign in fully developed phlebitis.

We will mention the possible mechanism that could take place to produce the cuff sign. The venous hypertension determined by the compression of the thigh produces in a few minutes a distention of the subjacent venous system, which induces the same painful effects that the tests, now in use, arouse by mechanical external influences.

It is likely that the artificial venous hypertension is a selective and subtle mechanical way to explore a very complex anatomic region, such as the neighboring structures of the deep venous vessels of the leg, in which, the external exploratory compressions, the stretching of the muscles by the clinician, as well as the muscular reflexes, the arteriovenous spasms, the extension of the inflammatory process of the vein to the neighboring nerves, the anomalies of the referred pain, the pain threshold, and the characteristics of the psychosomatic personality, require a very complicated analysis, sometimes impossible to perform.

The fact that the venous walls have an exquisite sensibility to pain caused by widening of the venous lumen, even instantaneous, has been proved by the studies of Louvel and associates.[36] The "cuff pain," found in patients with thrombophlebitis, specially in the veins adjacent to the root of the thigh, without being a constant or pathognomonic sign, confirms the mechanism existing in the painful response we produced with the cuff.

In our small series of patients with phlebitis, besides the inflammatory process in the majority of them, the veins did not have any old lesions or obstacles to the venous flow, and the hypertension provoked by the cuff must have been felt undoubtedly in all the distant venous territories, in some parts simply by plethora and distention. The interplay of constricting or dilating reflexes deserves some discussion.[75-83] The inflammatory reaction of the venous walls seems to make them very sensitive to the slightest eccentric distention derived from the increased venous volume; the venous reflexes seem to play no role in our exploratory technique, since a few seconds are enough to relieve the distress, contrary to painful vascular spasms that do not subside so rapidly.

The pain initiated or enhanced by the cuff cannot be ascribed to compression of the nerves of the thigh. It is true that the mechanical compression of the nerve pathways simulates the sensibility disturbances produced by arterial occlusion, but the compression affects the proprioceptive and tactile sensations before impairing the small fibers conducting the sensations of cold, heat, and pain. Numbness, itching, and cramplike sensations are only observed if the

compression is very prolonged or the patient has a diminished arterial flow in the legs, and the pain thus produced does not disappear in a matter of seconds.

The cuff sign is not positive in patients with varicose veins as would be expected, considering the anatomic condition of the coat of the veins revealed by the different tests performed in these patients, routinely. The Perthes test produces an increase in venous pressure far superior to the one determined by our test, and the Brodie-Trendelenburg test though similar is painless.

We did not consider it harmless to measure directly the venous pressure existing in our patients with phlebitis; the slight distention of the superficial veins, sometimes hardly noticeable, made us suspect only a slight increase in the venous pressure.

That there could be some cases with thromboangiitis obliterans in which the cuff sign is positive seems natural because of the possibility of spreading the arterial process to the deep satellite veins, the participation of arteriovenous reflexes, the weak venous flow induced by the reduced movements of the affected limbs, and the pathologic changes of the venous endothelium as a result of all these factors.

The cuff test, in a case of occlusion of the cephalic vein, was negative, corroborating the requisite of an inflamed venous coat to condition a painful distention.

SUMMARY

1. Fifty-eight patients were studied: thirty-two with phlebitis of the deep veins of the lower extremities; six with varicose veins, twelve with arteriosclerosis of the lower extremities, four with thromboangiitis obliterans disease, two with postphlebitic disturbances and two with nonspecific venous disturbances.

2. A new test to explore the deep veins is proposed, by means of a cuff applied to the thigh and inflated to a pressure of 4 cm. Hg; the special pain thus provoked in the patients with phlebitis is described.

3. The authors found this sign to be positive in 100 per cent of the cases in comparison with the Homans sign that was positive only in 81.2 per cent. The results are compared with other tests currently in use. The new sign is called the "cuff sign."

4. The possible mechanisms of this new sign are discussed.

SUMMARIO IN INTERLINGUA

1. Esseva studiate 32 patientes con phlebitis del venas profunde del extremitates inferior, 6 con venas varicose, 12 con arteriosclerosis del extremitates inferior, 4 con thromboangitis obliterante, 2 con disturbationes postphlebitic, e 2 con non-specific disturbationes del venas.

2. Es proponite un nove test pro explorar le profunde venas. Illo consiste in le application al femore de un bracial pneumatic inflate a un pression de 4 cm Hg. Es describite le dolor special que resulta in patientes phlebitic.

3. In le experientia del autores iste signo esseva positive in 100 pro cento del casos durante que le signo de Homans esseva positive solmente in 81,2 pro

cento del casos. Le resultatos es comparate con altere tests que es currentemente in uso. Le nove signo es appellate le "signo bracial."

4. Es discutite le possibile mechanismos del nove signo.

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ELECTROCARDIOGRAPHIC CHANGES DURING MITRAL COMMISSUROTOMY

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DESPITE the great number of surgical operations performed in the past few years for the relief of mitral stenosis there is a surprising paucity of published observations on the electrocardiographic changes associated with the procedure. We are aware of only two publications dealing primarily with this subject, one based upon twenty-four,[1] the other upon sixty cases.[2] The present report summarizes experience with the first 100 patients subjected to mitral commissurotomy at Montefiore Hospital. The operations were performed by the surgical members of the cardiovascular team. This experience includes the frequent use of antiarrhythmic and antihypotensive drugs. It has been our practice to perform cardiac surgery under continuous electrocardiographic monitoring by a member of a cardiovascular team. The purposes of this paper are to describe the behavior of the heart during operation, to evaluate the use of the previously mentioned drugs, and to assess the value of electrocardiographic monitoring during operation.

MATERIAL AND METHOD

The patients were carefully selected for surgery on the basis of disability attributable to pure or predominant mitral stenosis. According to Harken's[3] classification there were twenty in Class II, fifty-seven in Class III, and twenty-three in Class IV. All but four who were operated upon early in the series were fully digitalized at the time of operation and were deemed to be in an optimal state of compensation commensurate with their disease. The youngest patient was 19 years of age, and the oldest, 58. Ten were over 50 years old. Preoperatively normal sinus rhythm was present in forty-three and atrial fibrillation in fifty-seven patients.

Continuous monitoring was carried out by observation of the image on a Sanborn Cardioscope or a Cathode-ray oscilloscope.* When graphic records were desired, the circuit was switched to a Sanborn Viso-Cardiette. Continuous oximetric determinations were recorded on a Waters-Conley oximeter.

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*Part of a multiple-channel recording device specially built by Electronics for Medicine, Inc., New York, N.Y.

Patients were premedicated with morphine or morphine and secobarbital sodium. Atropine was also given in the earlier group of patients, but was later discontinued because of the occasional development of tachycardia preoperatively. Induction of anesthesia was accomplished with Thiopental sodium or secobarbital sodium and maintenance was carried out with 50 per cent nitrous oxide and 50 per cent oxygen with ether. Intubation was accomplished with topical five per cent cocaine in 60 patients, nitrous oxide and ether in twenty-four, cyclopropane in eleven, and a muscle relaxant was added in five (d-Tubocurarine or Flaxedil).

RESULTS

Electrocardiographic changes were found in all the patients at various times during the procedure. In addition to arrhythmias these included variations in amplitude and form of atrial and ventricular deflections, depression of RS-T segments, changes in form of T waves, and minor alterations in rate. No constant relationship of RS-T segment depression to arterial oxygen saturation or blood pressure level was found.

The most striking and most common change was the appearance of arrhythmias at one or more stages of the operation (Table I). In general the frequency and severity of arrhythmias increased in the later stages when physical manipulation of the heart and the actual commissurotomy were being done. During induction and intubation the arrhythmias were generally benign, consisting of minor alterations of rate due to disturbances of the S-A or A-V node or to occasional ventricular premature systoles.

TABLE I. FREQUENCY OF ARRHYTHMIAS DURING STAGES OF THE OPERATION

ARRHYTHMIA	NO. OF PATIENTS	INDUCTION	ENDOTRACHEAL INTUBATION	MANIPULATION OF HEART AND PERICARDIUM	COMMISSUROTOMY
Sinus tachycardia	6		4	3	3
Sinus bradycardia	3	3		1	1
A-V block	4	1	1	1	1
Nodal rhythm and interference dissociation	9	4	2	3	2
Atrial premature systoles	7		1	6	6
Nodal premature systoles	1			1	
Supraventricular tachycardia	9	2		6	3
Atrial flutter and fibrillation	5		1	3	2
Ventricular premature systoles	62	9	13	40	33
Ventricular tachycardia	44	1	3	17	41
Ventricular flutter and fibrillation	4		1	2	3

Ventricular premature systoles of increasing frequency and ventricular tachycardia were the commonest irregularities and were definitely associated with mechanical stimulation of the heart and stretching or occlusion of the mitral orifice. Often they subsided almost immediately after the mechanical stimulation ended without the use of cardiac drugs. There were five operative

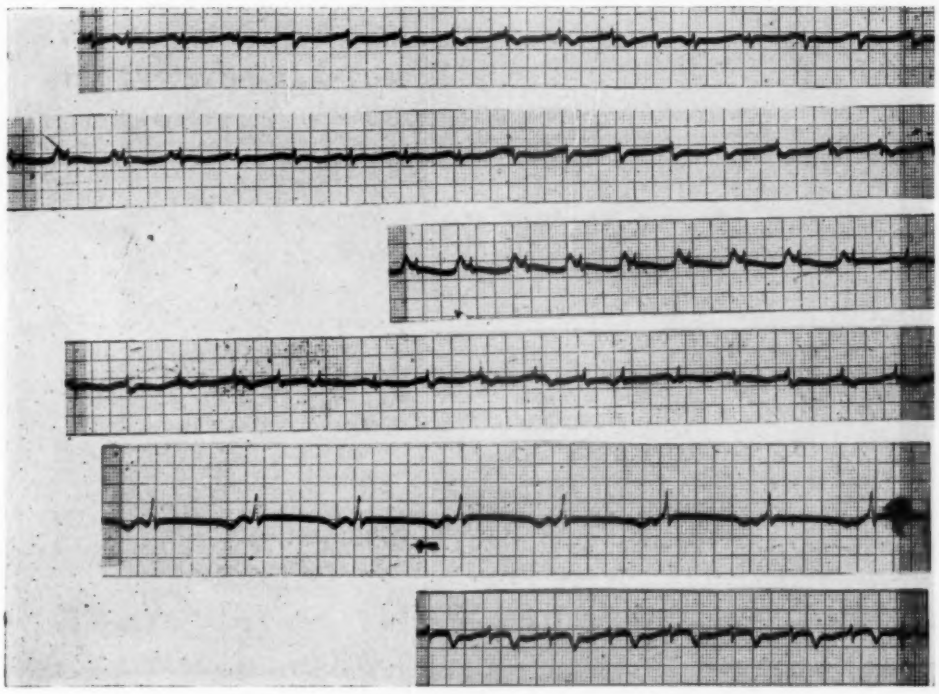

Fig. 1.—All strips are Lead II. Normal sinus rhythm with prolonged A-V conduction followed by interference dissociation (strips 2 and 3), lower nodal rhythm (strip 4), interference dissociation and lower nodal rhythm (strips 5 and 6).

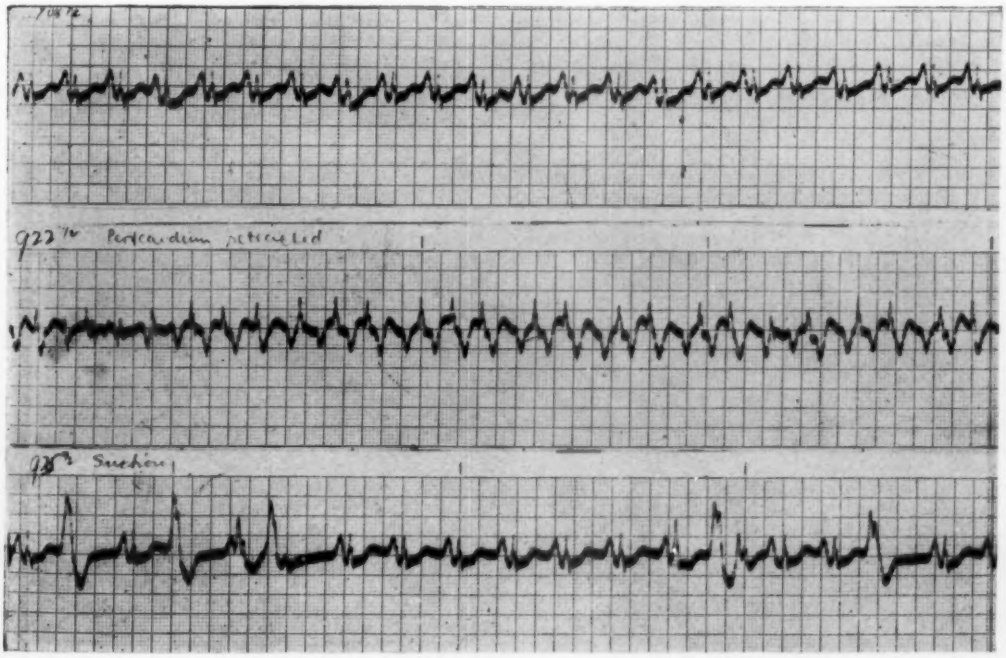

Fig. 2.—Two examples of high-grade ventricular tachycardia.

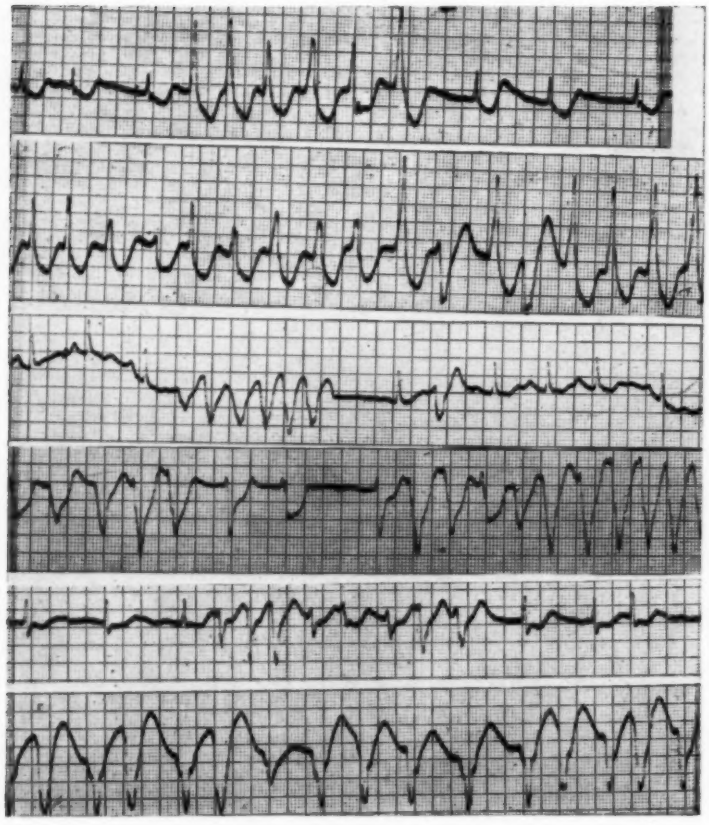

Fig. 3.—Five examples of "irregular ventricular tachycardia" associated with obstruction of the mitral orifice or the act of commissurotomy. The first two strips are of the same patient. All strips are Lead II.

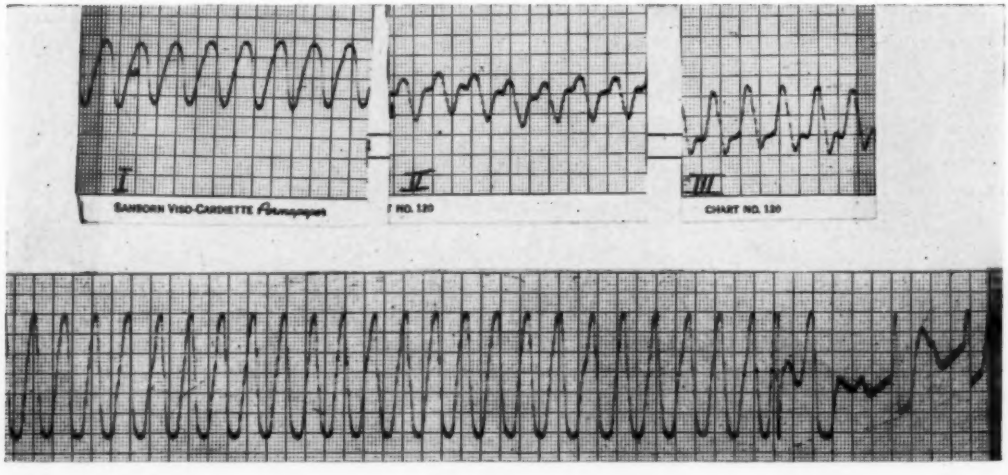

Fig. 4.—All strips are Lead II. Manipulation of the pericardium. Sinus tachycardia (strip 1) followed by atrial tachycardia with varying A-V block (strip 2), ventricular premature systoles and restoration of normal sinus rhythm on cessation of manipulation (strip 3).

deaths, the terminal rhythms being ventricular fibrillation in three, idioventricular rhythm and arrest in one, and ventricular tachycardia and arrest in one. Four mortalities occurred in Class IV patients and one in a Class III patient.

Specific cardiac treatment was undertaken only when an arrhythmia was unduly prolonged or when a protracted fall in blood pressure occurred. Twenty-eight patients were so treated (Tables II and III). In some instances several drugs were given concomitantly. About three-fourths of the patients received no drugs other than the anesthetic agents.

TABLE II. EFFECT OF VASOPRESSOR AGENTS

DRUGS	NO. OF PATIENTS	INDICATION	RESPONSE	REMARKS
Norepinephrine (Levophed)	20	18 Hypotension	13 Good 4 Poor 1 Died	1 Ventricular bigeminy 2 Ectopic beats with increased ventricular rate
		2 Hypotension and hemorrhage	2 Died	
Methoxamine HCl (Vasoxyl)	1	Hypotension	Poor	
Neosynephrine	1	Hypotension	Good	

TABLE III. DRUGS USED FOR ARRHYTHMIAS

DRUGS	NO. OF PATIENTS	INDICATION	RESPONSE	REMARK
Procaine amide (Pronestyl)	9	Supraventricular tachycardia Atrial tachycardia Supraventricular bigeminy Irregular ventricular tachycardia Ventricular bigeminy	0 0 0 Good 0	Died
K. Acetate	2	Ventricular premature systoles	0	
Digitalis	4	3 Atrial fibrillation with rapid ventricular rate 1 Supraventricular tachycardia	2 Good 0	
Quinidine	3	Ventricular premature systoles	Good	
Sodium thiobarbiturate (Pentothal)	2	Sinus tachycardia Supraventricular tachycardia	0 Good	
Neostigmine (Prostigmine)	1	Sinus tachycardia	Good	Transient asystole

DISCUSSION

It is worthwhile to review the changes during the various stages of operation. During induction important arrhythmias rarely occurred. In intubation the changes observed were of the same type as in induction but occurred more frequently. The arrhythmias developing during intubation have been attributed to vagovagal reflexes,[4] depth of anesthesia, anoxia, and carbon dioxide excess among other causes. In the hands of a skilled anesthetist arrhythmias lessened when "bucking" on the tube with its resulting hypoxia, and respiratory acidosis was prevented.[5]

One patient developed an idioventricular rhythm during intubation, then a ventricular arrhythmia that could not be controlled and ended fatally. This was one of the two rare anesthetic deaths. Obviously there is danger of serious arrhythmias during intubation especially in patients with advanced underlying heart disease.

Maintenance of anesthesia did not offer a problem. Difficulty arose only when instrumentation or manipulation of the pericardium, myocardium, or valve caused a fall in blood pressure, arrhythmia, or both. Tachycardia was often associated with a fall in blood pressure especially when chronic anoxia was present due to advanced heart disease. This situation, if it persists, requires treatment since patients with tight mitral stenosis do not long tolerate a fall in blood pressure. Reduced cardiac output or increased left atrial pressure often develops. The former may cause shock; the latter, pulmonary edema. In such instances it is of the utmost importance to complete the operation before irreversible changes occur.

In our experience the most important arrhythmias occurred in association with insertion of the finger into the mitral orifice and during actual performance of the commissurotomy. Bursts of premature systoles and paroxysmal tachycardias, usually of ventricular origin, occurred in almost all cases. This has been noted by others.[1,2] Such changes are not difficult to understand as there is not only mechanical stimulation of highly sensitive cardiac tissue, but also marked anoxia resulting from complete cessation of the circulation when the finger is in the mitral orifice. The serious ventricular arrhythmias and hypotension contingent upon this procedure usually disappeared upon removal of the finger or completion of the commissurotomy.

In forty-four of our patients ventricular tachycardia developed during operation. The paroxysms varied in duration from a few seconds to several minutes, were sometimes intermittent and sometimes continuous, and occasionally of multifocal origin. Twenty-two of these cases were not treated, and the operations were successfully completed without the use of drugs. Only those cases were treated in which the paroxysms were prolonged or were accompanied by distinct hypotension (Tables II and III). It follows that even in ventricular tachycardia with hypotension resulting from manipulation, there is no cause for concern, providing that this phase of the operation is completed quickly, before changes develop that perpetuate arrhythmia and hypotension.

In many instances the ventricular tachycardia was markedly irregular. This arrhythmia appeared in patients with normal sinus rhythm as well as in those with atrial fibrillation. Also it was often preceded and followed by isolated ventricular premature systoles of similar form to the ventricular deflections during the tachycardia. Therefore, we designated the arrhythmia as "irregular ventricular tachycardia." Campbell and Reynolds[2] have also been impressed by this type of ventricular tachycardia.

Among the rarely observed changes were some surprising alterations of rhythm. In one case atrial fibrillation reverted to normal sinus rhythm, and in two, atrial fibrillation changed to flutter. However, these were all transient and were succeeded by atrial fibrillation within a few minutes. These changes occurred without the influence of drugs, and we are unable to explain them.

A 1 per cent procaine solution in the pericardium has been said to abolish ventricular ectopic beats and to decrease myocardial irritability upon manipulation.[6] In our first 100 patients one or more drugs were administered in twenty-eight. On the whole the results were disappointing. Restoration of the basic rhythm with intravenous procaine amide was rarely accomplished. Most successful was the use of norepinephrine in combating a fall in blood pressure, but in three patients the drug increased the ventricular arrhythmia and in another it induced this arrhythmia. In tachycardia of supraventricular origin and in atrial fibrillation Spiegel and associates[1] used neostigmine in fifteen of twenty-four reported cases and were favorably impressed with its action. Though we have had little experience with it, we feel the drug appears deserving of use.

Many patients can be managed without drugs. As experience progressed this became more apparent, so that of the 100 cases almost three-fourths received no drugs other than the anesthetic agents.

In patients with heart disease it was natural for us to seek relationships between anoxia manifested by fall in oximeter readings, and blood pressure levels and RS-T depression. No such links were found. There was, however, the well-established relationship between tachycardia and RS-T depression, independent of anesthesia or surgical technique.

There appeared to be no correlation between the age or clinical condition of the patients and the development of arrhythmias of various types. Nor can the influence of digitalization upon the development of arrhythmias be estimated since practically all the patients in this series were fully digitalized at the time of operation.

THE PLACE OF THE CARDIOLOGIST

Electrocardiographic observation during major surgery and especially during commissurotomy is of distinct value. Changes in rate and rhythm during cardiac surgery can often be detected only by the electrocardiograph. It is an established fact that such changes are frequently missed by the clinician or anesthesiologist. In so simple a matter as the rate of the heart a fairly large proportion of the beats may be missed by the palpating finger. Ziegler[7] reports that of 80 per cent of arrhythmias revealed by the electrocardiograph, only 6.5 per cent were recognized by ordinary means.

Fortunately in most cases this loss of accuracy is not important in the clinical course and need cause no concern, but because it is not possible to foretell which minor arrhythmia will lead to a serious one and because similar electrocardiographic changes may occur in every phase of operation, continuous knowledge of the electrical activity of the heart is important. An arrhythmia, whether supraventricular or ventricular, if it lasts long enough may result in a dangerous fall in blood pressure, progressive anoxia and shock with possible fatal termination.

Most probably it is not the arrhythmia per se, but the shock consequent to the arrhythmia which is of the greatest importance. This, of course, will be recognized by the anesthesiologist and treated irrespective of the electrocardiographic inscription at that time. Basically, it is of little significance whether at such a time the arrhythmia is ventricular or supraventricular in origin. In fact, frequently the experienced cardiologist is unable to tell this either at the time of inscription or later with many hours to ponder over the record.

Thus, since the anesthesiologist can watch the blood pressure and the rate and rhythm of the heart and cope with shock, it appears to us that most cases could easily be managed without a cardiologist. The surgeon can handle cardiac arrest and ventricular fibrillation. The place of the cardiologist is chiefly in the selection of patients for operation and in the preoperative and postoperative management of arrhythmias, congestive failure, and carditis.

SUMMARY

1. Continuous electrocardiographic observations were made on 100 patients undergoing mitral commissurotomy.

2. Changes occurred in every case and included practically every known abnormality of rate and rhythm, as well as variations in form and amplitude of atrial and ventricular defections.

3. The most frequently encountered serious arrhythmia was ventricular tachycardia (44 cases), usually irregular and associated with occlusion of the mitral orifice by the surgeon's finger.

4. In three-fourths of the cases it was unnecessary to use any drugs. Indeed, only one-half the cases of ventricular tachycardia were treated. The best response to drug therapy resulted from the use of vasopressor agents.

5. No constant causal relationship was found between blood pressure or oximetric determinations and RS-T deviations.

CONCLUSIONS

1. Most of the arrhythmias appearing during mitral commissurotomy are surprisingly benign and rarely require heroic pharmacologic measures.

2. The prevention of shock is probably more important than the control of arrhythmias.

3. Continuous electrocardiographic monitoring is very helpful, but it is not necessary for a cardiologist to be present at every operation.

SUMMARIO IN INTERLINGUA

Es presentate un revista del experientias in 100 commissurotomias executate pro stenosis mitral. Il es interessante notar que arrhythmias, ben que frequente, esseva usualmente benigne, excepte durante manipulation del corde e durante le obstruction del orificio mitral per le digito del chirurgo. Iste arrhythmias cessava in le majoritate del casos quando le manipulation del corde habeva cessate o quando le commissurotomia esseva completate. Drogas vasopressor esseva de adjuta in hypotension e associate arrhythmias. Nos opina que le contribution principal del cardiologo non consiste in le surveliantia electrocardiographic del operation mesme sed plus tosto in le selection del patientes con bon prognoses chirurgic e in lor observation pre- e postoperative.

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VARIATIONS IN DIRECT SPATIAL VECTORCARDIOGRAMS RESULTING FROM ALTERED PLACEMENT OF ELECTRODES IN THE CUBE SYSTEM

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INTRODUCTION

THE purpose of this study is to determine what effect alteration of the position of one or more of the electrodes within the cube system would have on the direct spatial vectorcardiogram.

Other reported studies in direct spatial vectorcardiography primarily deal with cardiac abnormalities,[1-5] technical advances in the projection and recording of the vectorcardiogram,[6-8] and discussions of the merits of the systems of electrode placement.[9-11] Primarily two systems are employed: one embodying the principles of the equilateral tetrahedron; the other, the principles of the cube.

Grishman and Scherlis, using a modified Duchosal-Sulzer cube placement, have reported on the effect of deep inspiration and expiration on the direct spatial vectorcardiogram.[10] A search of the literature, however, fails to reveal any report on the effect of small to moderate variation in the placement of individual electrodes within either system.

MATERIALS AND METHODS

The subjects were patients from the wards of the Los Angeles County Hospital. Eight patients were studied whose clinical history, physical examination, electrocardiogram, fluoroscopy, and chest x-rays failed to indicate any evidence of heart disease. Their ages ranged from 26 to 59 years. Two were females and six were males. Electrocardiograms were recorded on the string galvanometer at a speed of 25 mm. per second. In addition to the conventional leads, Lead V_{3R}* was taken. The electrocardiograms of the same patient were taken within a period of 24 hours.

The vectorcardiograms were obtained using the method described by Grishman and Scherlis based on their modification of the Duchosal-Sulzer cube arrangement for the placement of the electrodes. Only one oscilloscope was used, so arranged that each plane could be obtained with push-button rapidity.

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*Precordial electrode placed in V right intercostal space at the midclavicular line.

The vector loop was interrupted 400 times per second by intensity modulation which produced arrow-shaped segments. This permitted time analysis of the loop and determination of the direction of movement since the point of the arrow indicated the direction in which the loop was inscribed. The loops were photographed on fast film using a camera set for time exposure. Several loops were recorded in the same plane on the same film by moving the position of the loop on the face of the oscilloscope.

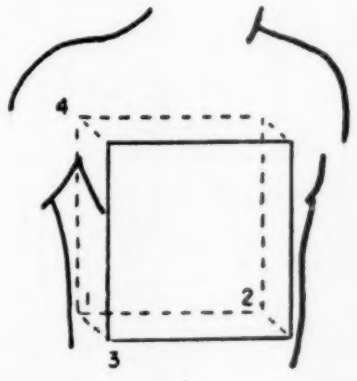

Fig. 1.—Normal electrode placement (From Scherlis and Grishman[3,5]).

RESULTS

Routinely, the electrodes were placed at the level of the second lumbar spine in the right anterior and posterior axillary lines, the left posterior axillary line, and on the posterior aspect of the right shoulder. (See Fig. 1 for position number of electrodes.) The vectorcardiograms of all the eight patients taken in this manner were normal. When the electrodes *1*, *2*, and *3* (Fig. 1) were moved caudad from level of T 10 to L 4 in stages of two vertebral widths, the horizontal QRS vector loop became narrower, smaller, and more anterior (Fig. 2). There was no significant change in the general configuration or rotation of the loop. The orientation and appearance of the T loop was not significantly altered. However, in three cases the orientation of the QRS loop was altered (See Discussion).

The frontal QRS vector loop became slightly smaller and more inferior. The orientation of the loop as viewed by the Einthoven Triangle Reference System or the Tri-axial Reference System of Bayley shifted toward the right axis but the general configuration and rotation remained unchanged (Fig. 2). This was particularly apparent between L 2 and L 4. The T loop, however, had no significant alteration of its orientation or configuration.

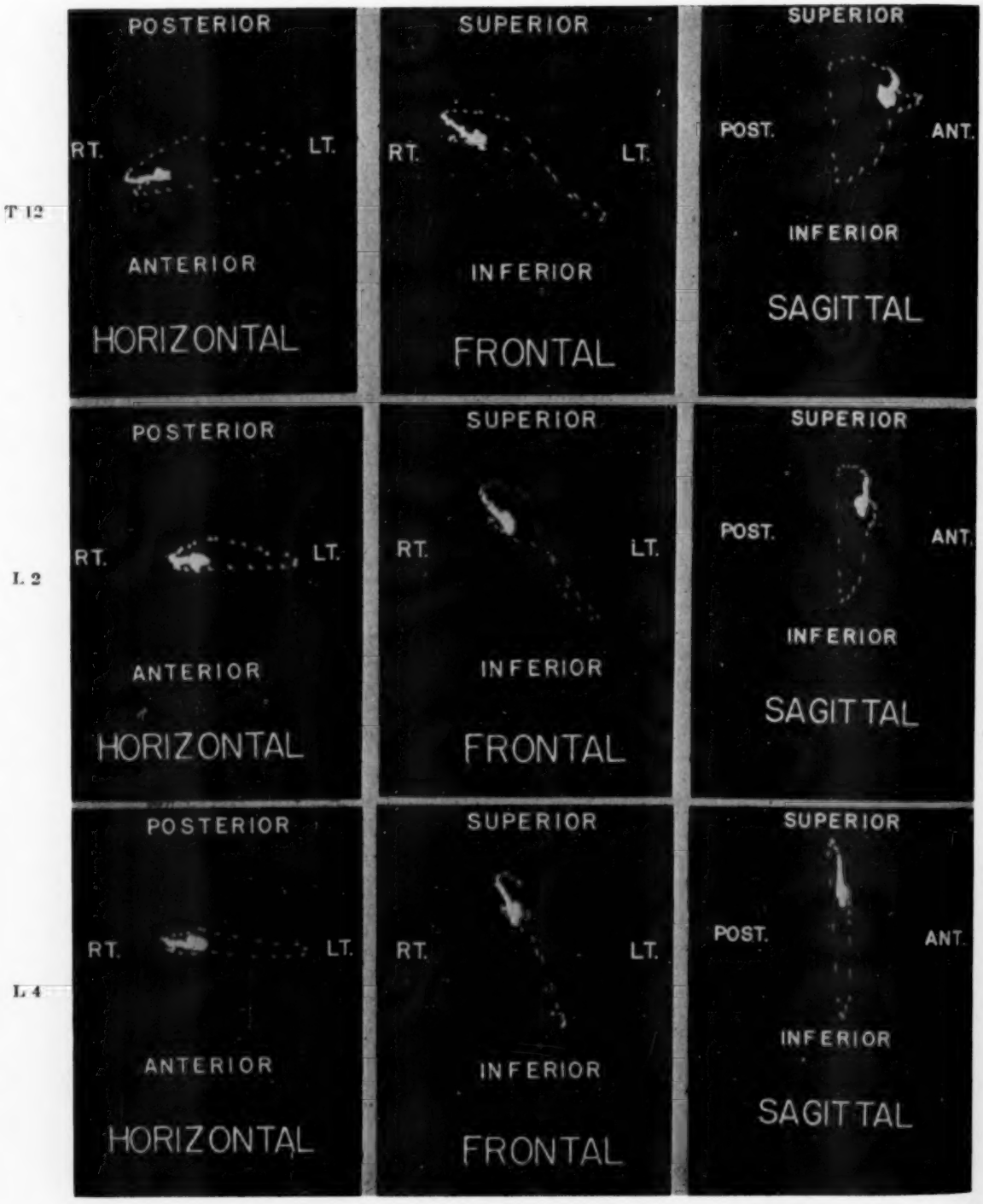

Fig. 2.—Normal vector loops showing slight anterior shift and narrowing as chest electrodes are moved caudad.

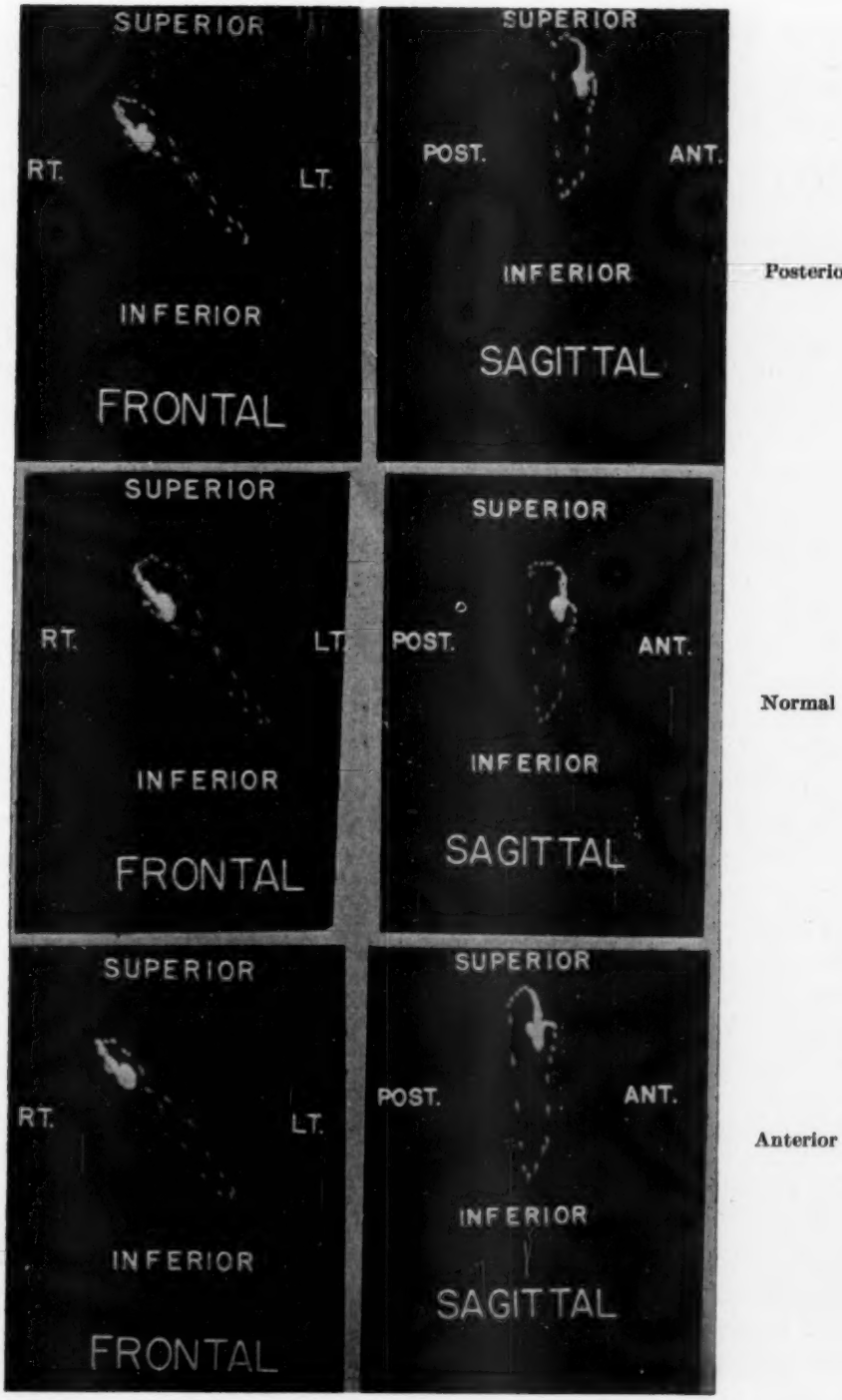

Fig. 3.—Normal vector loops showing slight variation as shoulder electrode is moved anterior or posterior.

Alterations were more apparent in the sagittal view. The QRS loop became narrower, more inferior, and longer. If a superior portion was present, it remained essentially unchanged. The increased length of the loop occurred in the inferior portion, thus increasing the proportion of the loop which was inferior. The narrowing of the loop occurred predominantly as the posterior limb approached the anterior limb more closely. This placed the loop in a slightly more anterior position, a finding consistent with that previously noted in the horizontal view. There appeared to be no significant change in the position, rotation, or general configuration of the vector loop. The T loop had no significant change (Fig. 2).

When the chest electrodes were fixed at the normal position at L 2 and the shoulder electrode moved anteriorly to the clavicular-acromial joint, the frontal QRS loop appeared slightly narrower; and the sagittal QRS loop was oriented more inferiorly (Fig. 3). These changes, however, did not significantly alter the general configuration of the loop. When the shoulder electrode was moved posteriorly to the midscapular area while the chest electrodes were maintained in the normal fixed position, a narrower frontal loop and slightly wider and shorter sagittal loop were produced. However, the general contour and configuration were not significantly altered (Fig. 3). Similarly when the right-chest electrodes were placed either closer or further apart while the shoulder and left-chest electrodes were maintained in the normal position the loops became slightly narrower and smaller as the electrodes approached each other, and slightly wider and longer as the electrodes were moved further apart. There was no significant change in orientation, contour, or rotation.

The effect of deep inspiration or deep expiration by the patient with the chest electrodes placed at various levels from T 12 to L 4 was observed. Deep inspiration produced slight narrowing of the horizontal and frontal loops and slight widening of the sagittal loop with the loop oriented slightly more posteriorly and inferiorly. Deep expiration produced the opposite effect on the shape and orientation of the loops. These changes were very slight and were similarly noted at each of the vertebral levels in each of the eight cases.

DISCUSSION

Shifting the shoulder electrode anteriorly or posteriorly between the clavicle and the mid-scapula produced no significant change with respect to proper interpretation of the vector as to its normality or abnormality. Widening or narrowing the distances between the right-chest leads produced no changes sufficient to confuse the interpretation. Furthermore, depth of respiration produced no significant changes in the vector loop thus confirming the findings of Grishman and associates.[10]

In three cases, however, placement of chest electrode positions at the level of T 12 produced changes worthy of special note. In this position the loops tended to be oriented more posteriorly, and in these cases this change was sufficient to produce a series of vectors suggesting early left ventricular hypertrophy (Fig. 4).

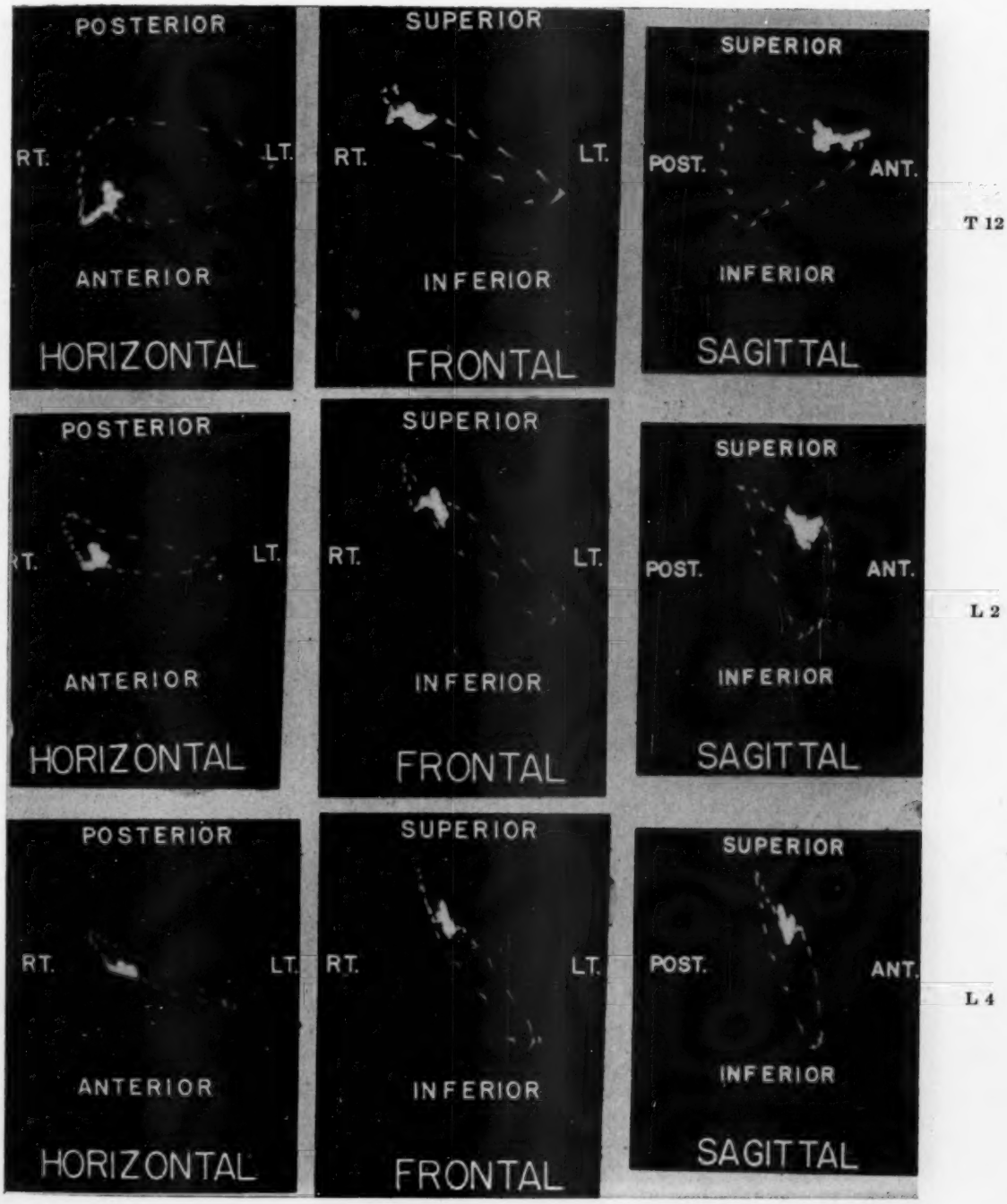

Fig. 4.—Normal vector loops with posterior displacement suggesting left ventricular hypertrophy at T 12. Anterior shift is noted as chest electrodes are moved caudad.

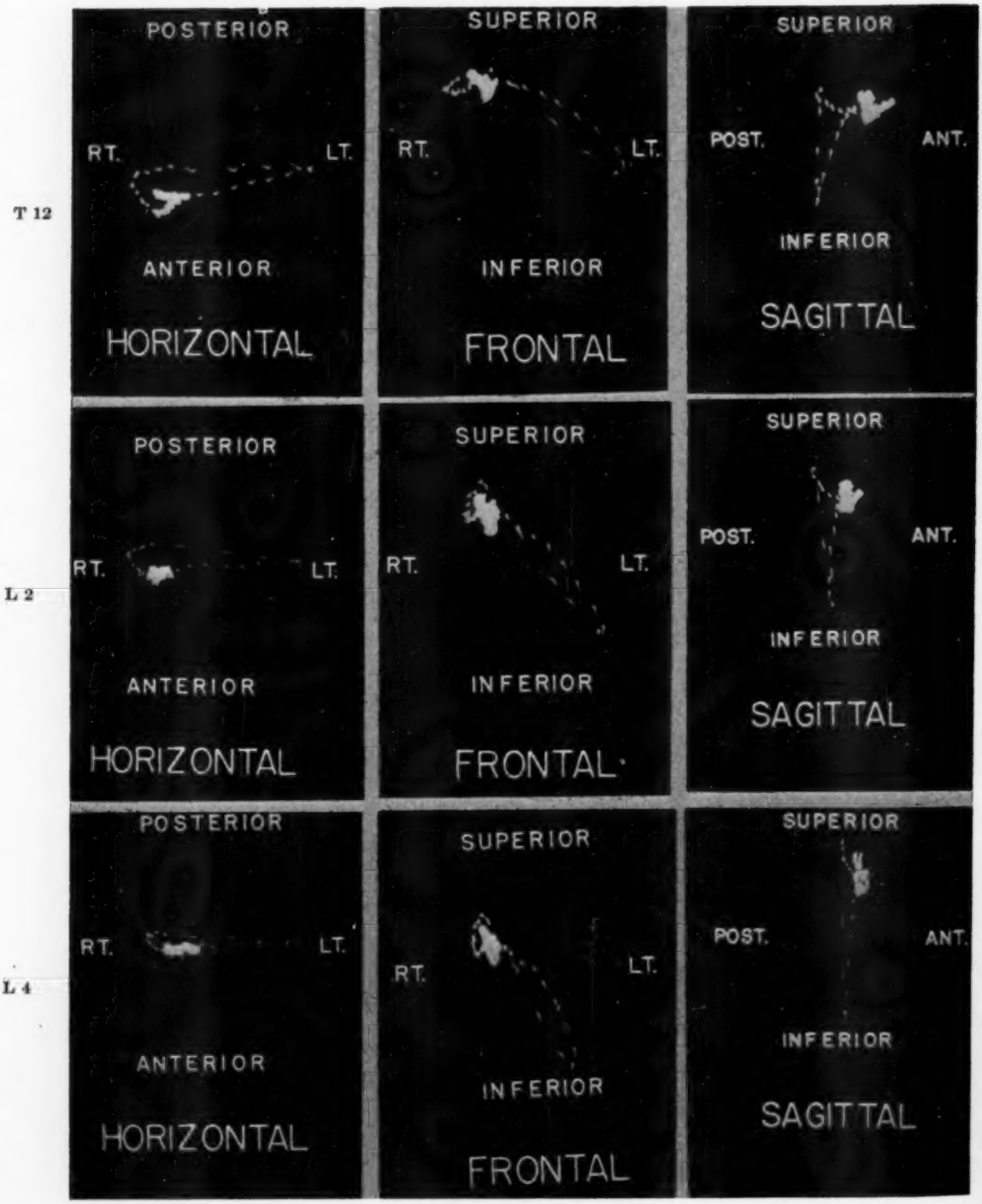

Fig. 5.—Normal vector loops with appearance suggesting early L.V.H. or anterior infarct at T 12, shifting to normal appearance as chest electrodes are moved caudad.

Furthermore, in one of these three cases, the vector loop, recorded with chest electrodes at T 12, so shunned the anterior region that the possibility of anterior infarction might well be entertained (Fig. 5), a finding inconsistent with the clinical and laboratory data.

In view of these findings a word of caution is indicated regarding accurate placement of chest electrodes with respect to the vertebral level. Reasonable care should be used to locate the second lumbar spine and to place the electrodes at this level. If this procedure is followed, it is unlikely that any significant alteration of the vector loops will result from electrode placement since the error in placement purposely induced in this series is roughly two to four times the length of the electrodes, an error not likely to result if reasonable precaution is taken.

SUMMARY

1. Eight patients with normal cardiovascular systems were examined by direct spatial vectorcardiography. In all cases normal vectors were noted when the usual electrode placement was used.

2. By varying the location of the shoulder electrodes, the distances between the right chest electrodes, and the depth of respiration, no significant changes were noted.

3. In three of eight cases, upon placing the chest electrodes at T 12 instead of L 2, vector loops suggesting early left ventricular hypertrophy were produced as a result of change in spatial orientation of the loops. In one of these cases a configuration suggesting anterior infarction was noted.

4. The need for proper placement of chest electrodes with respect to vertebral level is emphasized.

SUMMARIO IN INTERLINGUA

1. Esseva executate un studio de directe vectorcardiographia spatial in 8 patientes con normal systemas cardiovascular. In omne casos vectores normal esseva constatate quando le usual placiamento del electrodos esseva empleate.

2. Nulle significative cambiamentos esseva notate post variar le loco del electrodo spatular, le distantias inter le dextere electrodos thoracic, e le profunditate del respiration.

3. Post placiar le electrodos thoracic in T 12 (in loco de in L 2), il esseva notate in 3 inter 8 casos que spiras vectorial esseva producite le quales—in consequentia de un alteration de lor orientation spatial—pareva indicar le prime phases de hypertrophia sinistroventricular. In 1 de iste casos le configuration esseva de natura a suggerer infarcimento anterior.

4. Es sublineate le necessitate del correcte placiamento del electrodos thoracic in lor nivello vertebral.

The authors gratefully acknowledge the facilities and helpful direction of George C. Griffith, M.D., the editorial assistance of Robert W. Oblath, M.D., and the photographic advice of Mr. Lloyd Matlovsky.

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THE ORIGIN OF THE INITIAL NEGATIVE DEFLECTION IN THE RIGHT AURICULAR ENDOELECTROGRAM

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SINCE the discovery of the sinoauricular (S-A) node in the mole's heart by Keith and Flack in 1906, there has been a constant effort on the part of investigators and clinicians to find the electrocardiographic expression of the pacemaker activity in the mammalian heart. As the electrocardiograph is the best and most suitable instrument for analysis of the cardiac rhythm, direct electrocardiographic evidence of the S-A node activity in mammalians would be of obvious physiologic and clinical importance.

However, if one disregards the earlier and unconfirmed reports of Doxiades,[1] the research concerning man and some smaller mammals was unfruitful, and its failure was explained by the relatively small mass of the S-A node and consequently its inability to impress upon the extremities of the human or animal body measurable differences of electrical potential. Logically, therefore, the studies in question have been extended to larger mammalians. At a certain moment it seemed that, of all mammals, the horse, due to the size of its heart, possessed the important quality of allowing the direct electrocardiographic recording of the activation of its heart pacemaker in the limb leads. Indeed, Einthoven,[2] as it can be seen from the tracing obtained by him and published by Tchermak,[3] attributed the first positivity of the frequently diphasic auricular wave to sinus node potential and designated it by the letter "O". Subsequently this was confirmed by Noerr.[4] However, Kahn[5] cast considerable doubt upon such a concept, and, in view of the results of the recent study by the author,* the opinion of Einthoven[2] and Noerr[4] might be considered as incorrect. Also, it should be mentioned that Alfredson and Sykes[6] did not observe in their study of dairy cattle one instance of the notching of the P wave, and White and his associates[7,8] did not register the "O" wave in the electrocardiograms of the elephant and the beluga whale. Thus, the electrocardiograms of all mammals, big and small, do not show any sign of the sinus node activity in conventional and unipolar limb leads. This is in contrast to the electrocardiograms of cold-blooded animals, in which Eyster and Meek[9] observed a wave preceding the P

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*Les Endoelectrogrammes des Chevaux, (to be published).

wave of the limb electrocardiogram. The same authors sought the reasons for this striking difference in the inequality of anatomic and physiologic relations, as the sinus region forms a separate chamber in the cold-blooded vertebrates.

As was known to Eyster and Meek,[9] the situation changes as soon as one returns to direct leads from the neighborhood of the S-A node. In this study, if the exploring electrode were placed directly on the node of the dog's heart and the indifferent one on the left hind leg of the animal, an early negative potential appeared and preceded the P wave of Lead III by 0.01 sec. Therefore, it was considered by them as a sinus node wave. Moreover, according to Brown,[10] these facts have been confirmed by Wedd and Stroud,[11] and Eyster and Meek's[9] interpretation has been adhered to. It is not surprising, therefore, that, following the recording of intracardiac tracings and the description of the central terminal, new attempts at recording the activity of the pacemaker have been made.

In 1936, Brown[10] studied the esophageal lead in man. He established the presence of a very small negative wave starting about 0.018 sec. before the onset of the P wave in Lead II. In 1947, Battro and Bidoggia[12] designated the first negative deflection of the right auricular endoelectrogram by the letter "S" and attributed it to the activation of the sinoauricular node. In 1947, Sodi-Pallares and associates[13] attributed the negative deflection under consideration to an " . . . unequal distribution of the wave of excitation leaving the sinus node, resulting at a given moment, in predominance of the forces leaving the exploring electrode." These papers aroused interest in the inscription of the initial right auricular wave and were followed by studies attempting to determine further the conditions of its appearance. Groedel and Borchardt[14] in 1948 explored electrographically in man nearly the entire surface of the heart in patients to be submitted to pneumolysis. Their findings should be discussed, because of the fact (Sodi-Pallares,[15] Prinzmetal and co-workers[16]) that the electrograms from within and from without the atria do not show any appreciable differences.

Groedel and Borchardt[14] were able to confirm the existence of the negative initial potential or Q_a wave in the electrograms of the anterior wall of the right atrium near the sulcus terminalis. Nevertheless, as this wave was not separated from the R_a wave by an appreciable interval and did not precede the P wave in Lead II, they did not accept the opinion of a close relationship between this electrographic event and the S-A node. On the other hand they established in one of their cases the presence of the positive potential preceding the auricular complex by 0.02 sec. which was similar to what Hecht[17] found and termed in 1946 as a "pre-auricular" deflection. This could represent the electrical equivalent of S-A node activation according to Groedel and Borchardt,[14] and in agreement with the earlier and previously mentioned hypothesis of Hecht.[17]

In a more recent study of Levine and associates,[18] "consistent" positive preauricular potentials were not found. In contrast, the initial negative potentials were frequent in the right auricular endoelectrogram in man and have been submitted to a very precise analysis principally from the point of view of

sites from which they could be derived. It was shown that the Q_a wave could be recorded solely at high-median and mid-median levels of the exploring electrode in the right atrium. In lateral parts of the right atrium, as well as at low-median levels, the Q_a wave was absent. Furthermore, the appearance of the graphs was such as to suggest, according to Levine and associates,[18] that the latter part of the auricular endoelectrogram was a continuance of the initial negative wave Q_a, interrupted by the more rapid auricular deflection. The origin of the initial negative deflection remained doubtful in the opinion of the same authors.

The study of Kossman and associates[19] embraced, besides the spatial aspects of the Q_a wave, also its temporary relationship to other electrocardiographic events. The endoelectrograms and the electrocardiograms were also taken from human beings. Out of three cases studied, the Q_a wave was found twice at the upper part of the right atrium, and in one case, although inconstantly, it was recorded both at upper and lower levels. This wave occurred slightly earlier than or nearly simultaneous with the P wave of Lead I. Because of this, Kossman and associates[19] deny the sinoatrial origin of the wave in question. On a schematic representation of the right atrium in their paper, they explain that the position of the exploring electrode in some parts of the right atrium could be such that it was looking toward the tail of the wave of depolarization and presented a negative potential at the beginning of excitation, whereas a few hundreds of a second later it was being approached by the front of the wave of depolarization on the septal side of the atrium.

The latest comments in respect of the wave in consideration belong to Sodi-Pallares,[15] Luisada,[20] and Lenègre and associates.[21] Sodi-Pallares[15] points out that, in some experiments, the negative initial deflection did not appear in the right auricular endoelectrograms derived from points situated in the close neighborhood of the sinus node, whereas he was able to record it in the course of the same experiments at much lower levels of the right atrium. Luisada,[20] who with his collaborators was the first to obtain endocavitary leads in dogs by means of a catheter, mentions that the Q_a precedes the P wave of the limb leads by almost 0.05 sec. and, therefore, considers it as due to the sinus node activity. Lenègre and associates[21] stipulate that the greater distinctness of Q_a at sites nearer to the cardiac pacemaker is in favor of the point of view of Battro and Bidoggia[12] and of Brown.[10] In conclusion, it seems the Q_a wave is a somewhat inconstant event inscribed in the electrograms recorded either from the surface or from the cavity of the right atrium, as well as in the tracings recorded from the esophagus. Sometimes it precedes the P wave of the Leads I and II; sometimes, however, it commences nearly simultaneously with the electrocardiographic P wave of the conventional leads. It is definitely more frequent at higher levels, particularly in the paraseptal parts of the right atrium, although it could be also found sometimes at much lower levels. The influence of drugs upon its presence, size, or duration, as far as we know, has not been determined. Its origin is still obscure.

PROCEDURE

The data of this article have been obtained from four experiments on horses, one experiment on a mule, forty-three experiments on young bulls, and ten experiments on dogs. The experiments have been divided into four groups. Instead of taking into consideration the differences between the respective species, we have applied the criteria depending on the method inherent to each experiment and the study of some quality or another of the behavior of Q_a wave under previously determined conditions. Thus, in the first group of experiments we tried to establish the time relationship between the typically monophasic and negative auricular complex obtainable in the uppermost parts of the right atrium (representing according to Hecht[17] the potential variations of the S-A node region), and the Q_a wave appearing at a lower level of the right atrium. This was done by measuring exactly the auriculoventricular conduction time at both levels of the atrium, assuming of course that the moment of the onset of the ventricular complex must be about the same for the two nearby auricular points.

In the second group of experiments, we used two independent galvanometers, in order to establish time relations between the so-called "O" wave of the electrocardiogram and the Q_a wave of the right auricular endoelectrogram. In some experiments of this series, we have also compared various electric phenomena of the left-ventricular and right-auricular endoelectrograms, the latter on the level of Q_a wave. We include finally in this group five right auricular endoelectrograms (two of horses, one of a mule, and two of bulls), in which, after the end of the right-auricular complex beginning from the Q_a wave, the entire course of the left auricular complex was manifest and thus could be closely followed and analyzed. For the comparison of time of appearance of different electric phenomena in the two independent electric graphs, we have frequently identified the auricular and ventricular complexes by including simultaneous standardization marks, and the relations of the time lines of two independent galvanometers have been determined on the basis of the time intervals between two identical waves.

The third group of experiments was devoted to the study of the behavior of the Q_a wave under the influence of certain drugs. The drugs used were: digitalis, ouabain, khellin, Paveril Phosphate (dioxyline phosphate), antihistaminic compounds (Neo-Antergan) and procaine amide.

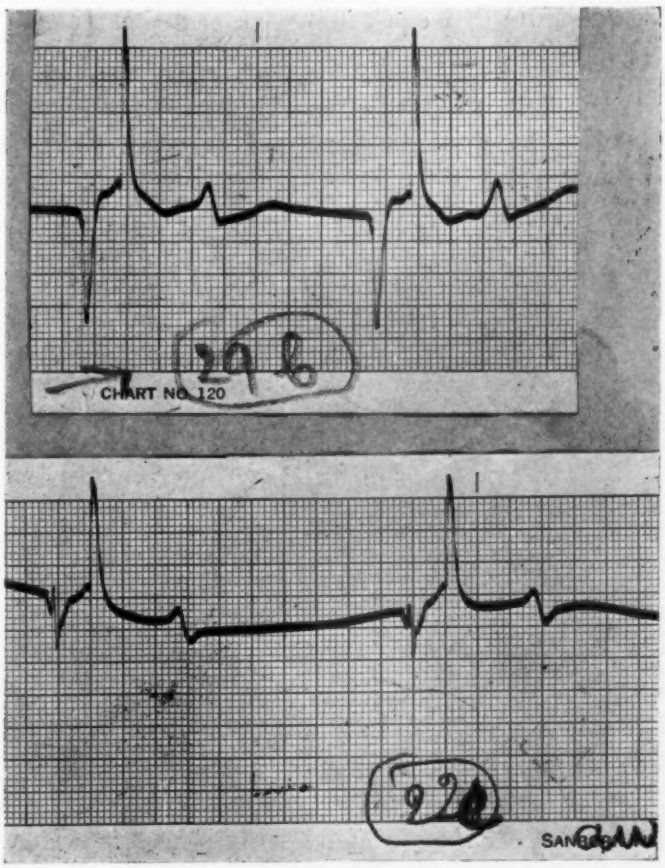
Finally, the fourth and last group of experiments was carried out on dogs and consisted of open chest experiments, in which some drug, mostly procaine amide, was injected into the right atrial cavity just above the exploring intracavital electrode or into the atrial wall above the epicardial electrode, in order to observe the behavior of the Q_a wave under the influence of the same drugs, but acting more locally.

The general technique was described in a previous communication. The large mammals (equine and bovine) were lying on one side on a wooden base which served as an electric insulator. After the bipolar and unipolar leads of the extremities had been obtained, we introduced through the external jugular vein a well insulated cable to the end of which had been soldered a small copper

ball of approximately 3 mm. in diameter. This ball was passed inside the right atrium and the different monophasic-negative, triphasic with Q_a wave, diphasic-plus minus-auricular complexes, were recorded and could be compared. In the three last groups of experiments, the cable was fixed by a hemostat to the wall of the dissected vein. This hemostat also held a needle through which various drugs could be injected.

In a few experiments, catheterization of the left ventricle was also carried out. An electrode similar to that used for the catheterization of the right half of the heart was employed, with the difference that, for this purpose, we put above the cable a flexible tube which could be moved along the cable and was installed in order to occlude the carotid artery and to prevent hemorrhage.

A.



B.

Fig. 1.—*A* and *B*, Auriculoventricular conduction time in the right auricular endoelectrograms of horse on the levels of QS_a and Q_a, respectively.

The technique adopted for dogs should be mentioned separately. The experiments on these animals belonged to Groups 3 and 4. In both cases artificial respiration had to be instituted and the chest opened. The pericardial sac was also opened by a broad triangular incision and its borders fixed to the

chest walls. At that moment drugs were introduced through the venous cannula or injected directly into the auricular cavity or subepicardially into the atrial wall.

A Sanborn Viso-Cardiette was used throughout. Sometimes a Cardiotron of the Electro-Physical Laboratories was also used.

RESULTS

Group 1: Time of Appearance of the Q_a Wave in Respect to the Monophasic Negative Auricular Complex (QS_a).—The experiments, carried out on equines (horses and mule), bovines (bulls), and canines (dogs), gave concordant and uniform results. The auriculoventricular conduction time in horses and in the mule, from the beginning of the Q_a wave to the onset of the ventricular complex, averaged 0.29 sec.; the same interval, from the onset of the totally negative complex to the Q wave of the ventricular complex did not surpass 0.28 sec. Again, for the auriculoventricular conduction time of the bovines, established at the level of Q_a and QS_a waves, the same figures were 0.14 and 0.13 sec., respectively. Finally, the few measurements determined in dogs gave the same results for both values, i.e., 0.12 sec. in both cases.

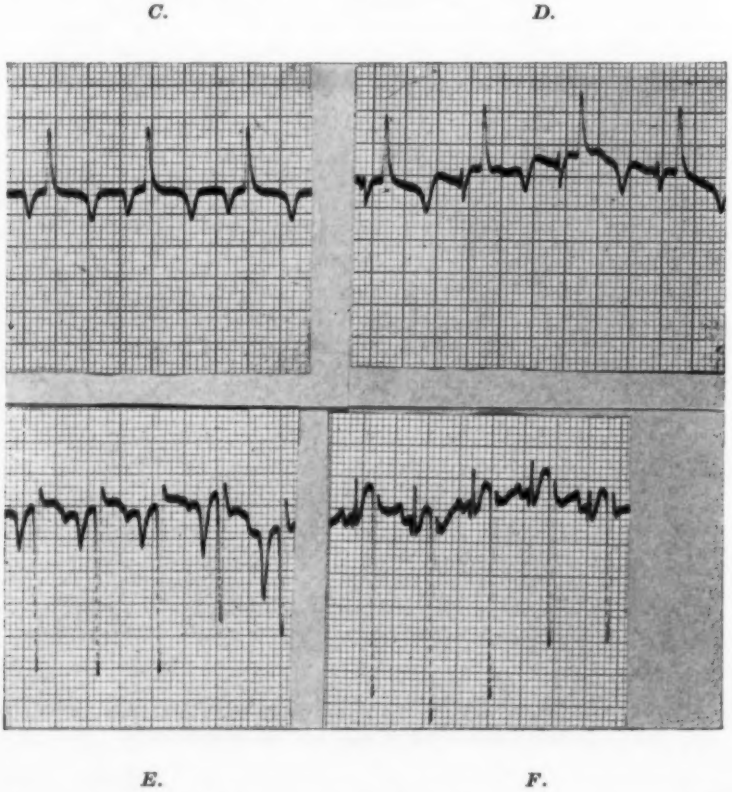


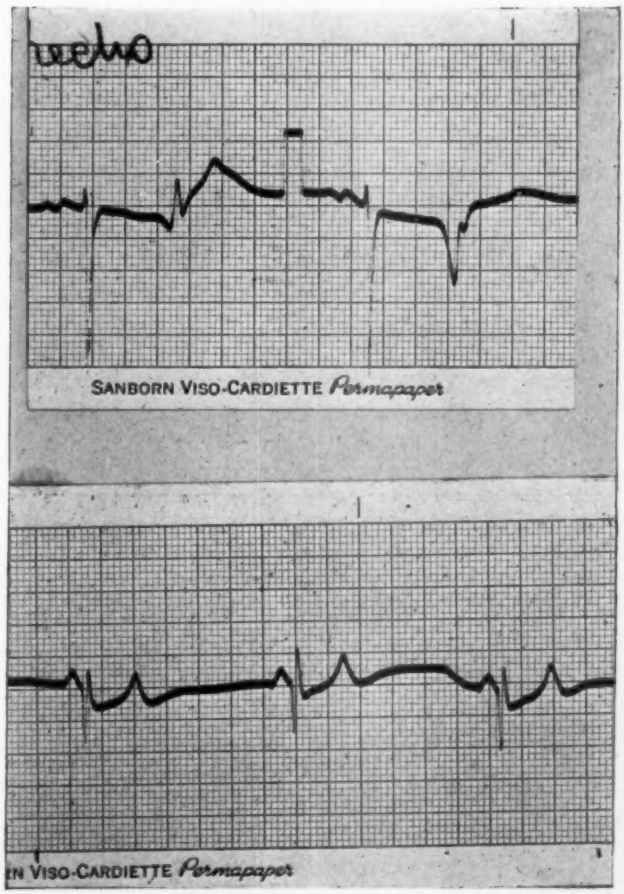
Fig. 1.—*C* and *D*, Auriculoventricular conduction time in the endoelectrograms of bull. *E* and *F*, The same in the endoelectrograms of dogs.

Fig. 1 will provide some examples. *A* and *B* belong to a horse, *C* and *D* to a bull, *E* and *F* to a dog. For further comparison we have added the right and

left ventricular endoelectrograms obtained from the same horse from which the right auricular endoelectrograms were derived. The auriculoventricular conduction time was in the two last instances 0.24 and 0.14 sec., respectively. Consequently, the conclusion seems warranted that the Q_a wave is the earliest possible part of the auricular depolarization in the right auricular endoelectrograms, as the ventricular complex has to begin simultaneously or even a fragment of a second earlier in the auricular endoelectrogram on the level of Q_a wave than on the level of auricular QS.

Group 2: Time Relations Between the Q_a Wave and the "O" Wave of Einthoven.[2]—These experiments were performed on equines only, because the

G.



H.

Fig. 1.—*G*, Right ventricular endoelectrogram of horse. Auriculoventricular conduction time, 0.24 sec. *H*, Left ventricular endoelectrogram of horse. Auriculoventricular conduction time, 0.14 sec.

notched auricular waves appear in physiologic conditions only in this species.* This series demonstrates that the Q_a or QS_a wave always precedes the "O" wave

***The only notable exception to this rule was the bull experimented upon on May 26, 1952. In that case the P wave was strongly negative in Lead I, positive and notched in Leads II and aV_R, positive in Lead III, and invisible in Leads aV_L and aV_F. We have assumed the presence of a congenital anomaly in the position of the heart on the basis of what is seen in human electrocardiography in cases of dextrocardia. However, autopsy was not performed for technical reasons.**

if the estimate is based upon the auriculoventricular conduction time. However, the ventricular complex may start earlier in the endoelectrograms or at the least simultaneously with the ventricular complex in conventional leads. The time interval between the "O" wave and the ventricular complex measured in the limb leads was in the majority of experiments (three horses and one mule) around 0.25 sec. The auriculoventricular conduction time in the right auricular endoelectrograms was on the average around 0.28 sec. (Fig. 2). Fig. 3 is also presented at this point in order to illustrate again the previously mentioned relations and to show the difference between the right and left auricular complexes. The values of the auriculoventricular conduction time were, respectively, for Lead aV_F (auricular complex beginning from "O") and for the right auricular endoelectrogram (auricular complex starting from Q_a) 0.16 and 0.20 sec. In regard to the two auricular complexes in the right auricular endo-

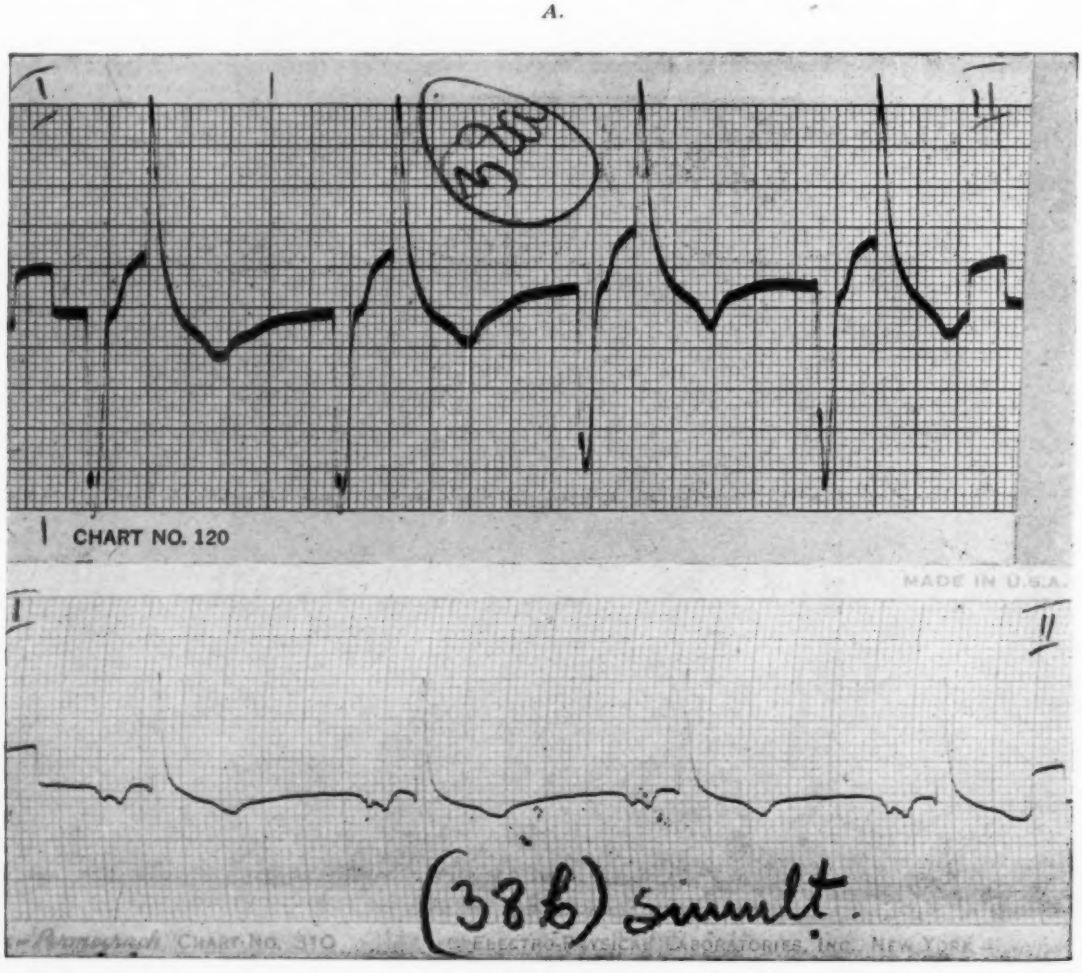


Fig. 2.—*A*, Right auricular endoelectrogram of horse. Auriculoventricular conduction time, 0.28 sec. *B*, Lead aV_L of the same animal simultaneously inscribed. Auriculoventricular conduction time (O-Q) 0.245 sec. The time marks of Cardiotron (Lead aV_L) represent an interval of 0.0378 sec., as the paper in this apparatus was running with a speed of 26.4 mm. per sec.

electrogram, it is difficult to assume we were dealing with a double auricular contraction (Prinzmetal and associates[16]), because this would be contrary to the law of the refractory phase of the heart muscle, and moreover Prinzmetal and his associates themselves admit that until now there are "no concomitant electrocardiographic data" in favor of such an interpretation. The second auricular complex represented, therefore, the depolarization of the left auricle

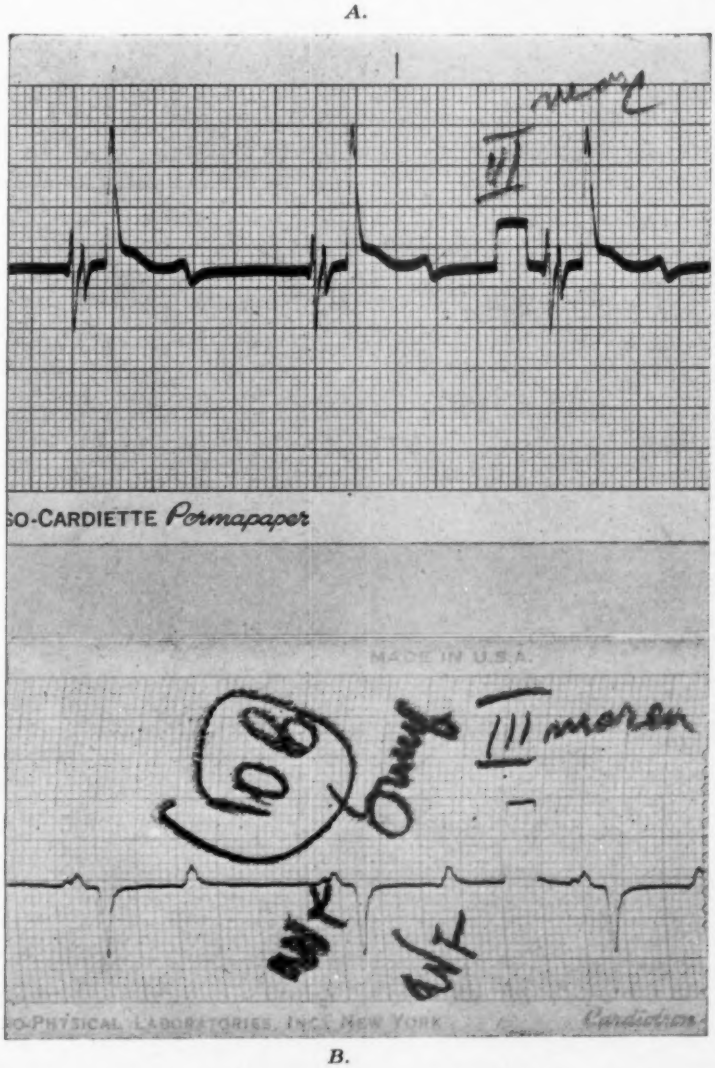
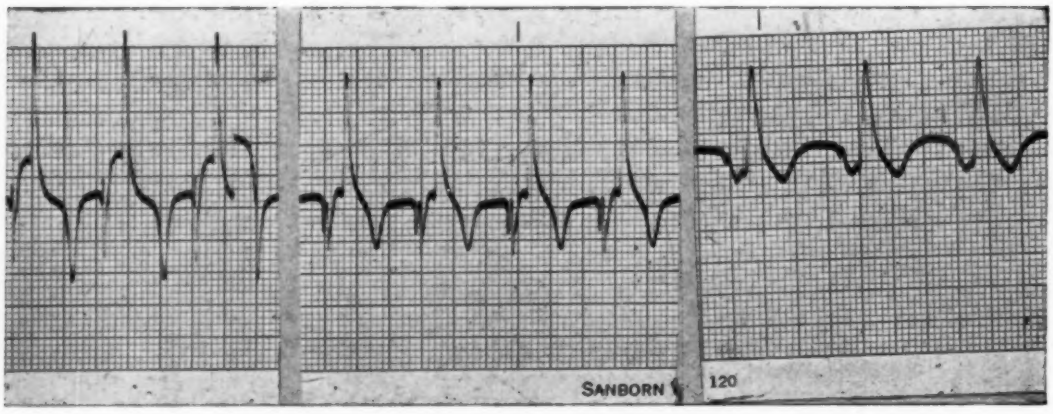


Fig. 3.—*A*, Right auricular endoelectrogram of horse with two auricular complexes. *B*, Lead aV$_F$ of the same animal simultaneously inscribed. The time marks of Cardiotron represent 0.0376 sec., as the paper was running with a speed of 26.5 mm. per sec.

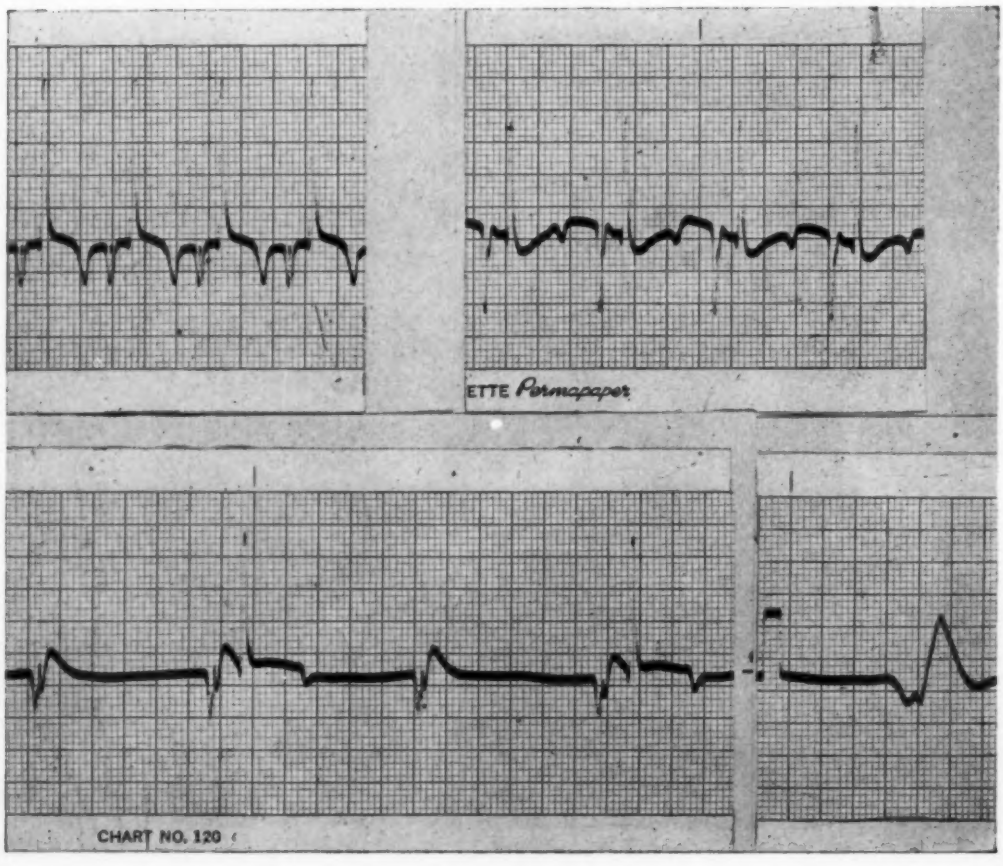
with the changes of the electrical potential transmitted passively to the right auricular cavity. It is interesting to note that, in the horse, the left-auricular activation starts apparently 0.07 sec. after the activation of the S-A node. In the dog, this interval is only 0.045 sec. (Rothberger).[22] Also it can be clearly seen that the depolarization of the left atrium takes place after that of the right



A. *B.* *C.*

Fig. 4.—*A*, Right auricular endoelectrogram of a bull. *B*, The same after the intravenous injection of 2 mg. of ouabain. *C*, The same after the injection of further 3 mg. of ouabain.

A. *B.*

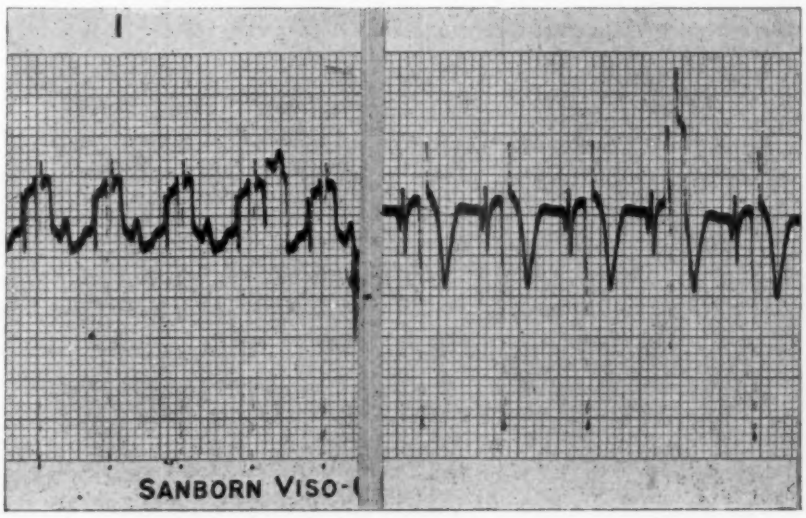


C. *D.*

Fig. 5.—*A*, Right auricular endoelectrogram of bull. *B*, The same after an intravenous injection of 10 c.c. of Neo-Antergan. *C*, The same after another injection of the same quantity of Neo-Antergan. A-V block 2:1. *D*, The same 10 minutes later. Complete arrest of ventricles.

is already completed. The main difference between the right and left auricular complexes is the presence in the former of the well delineated Q_a wave. The same happened in the other four experiments (two horses, one mule and one bull), in which we could observe two auricular complexes in the right auricular endoelectrogram. Thus the Q_a wave, as it seems, is the right auricular phenomenon at least under physiologic conditions and in the right auricular endoelectrogram.

Group 3: Influence of Drugs Slowing the Conduction of Impulses and Depressing the Frequency of the Heart Beat Upon the Behavior of the Q_a Wave.—These were the most numerous experiments in the present investigation. We carried them out in equines (horses and the mule), in bovines (bulls), and in canines (dogs). It seems important to mention that the drugs we administered induced bradycardia and inhibited the conduction in all species examined.



A. *B.*

Fig. 6.—*A*, Right auricular endoelectrogram of a dog. *B*, The same after the intra-auricular injection of 100 mg. of procaine amide immediately above the tip of the endoelectrode.

With reference to the Q_a wave the experiments in question gave uniform results to the extent that the drugs used did influence in the first place the amplitude of this wave and, to a smaller degree and in the later stage only, its duration. Thus, ouabain, digitalis, khellin, Neo-Antergan, procaine amide, and dioxyline (Paveril) phosphate augment as a rule the Q_a wave in the earlier stages of the intoxication. The typical course of such an experiment under the influence of ouabain is illustrated in Fig. 4. It can be seen that the Q_a wave exists in the beginning of the experiment, i.e., after the usual dose of barbiturates has been administered. After the injection of a large dose of ouabain the same wave is much more outstanding, because of the increase of its amplitude. Later on, and in preterminal stages, the Q_a wave amplitude suffers an obvious reduction.

In Fig. 5, the course of another experiment has been illustrated, in which we see the same changes under the influence of Neo-Antergan. At the beginning we had to deal with a clear Q_a wave which had an amplitude of 5 mm. and lasted 0.03 sec. The total duration of the auricular QRS was 0.055 sec. After the first injection of 10 c.c. of Neo-Antergan, the triphasic auricular complex became a QS_a wave, 12.5 mm. deep and lasting 0.055 sec. Following the next injection of the same quantity of drug, the triphasic auricular complex reappeared, the amplitude of Q_a wave was again 5 mm., its duration was 0.05 sec., while that of the initial part of auricular complex (QRS_a) increased up to 0.09 sec. Simultaneously a partial 2:1 auriculoventricular block was observed in the endoelectrographic tracing. At the end there was a complete arrest of the ventricles and the auricular QRS lost around 30 per cent of its original amplitude but lasted 0.14 sec.

The ultimate consequence of this course of events is a total separation of the Q_a wave from the main auricular complex which we have observed several times and reported in a previous communication.[23]

Group 4: Influence of Locally Administered Drugs Upon the Q_a Wave.— Four experiments altogether have been carried out in this series, two of them with the external unpolarizable $Cu/CuSO_4$ electrode and two with the intraauricular electrode. The last of these experiments performed with the intracavitary electrode is presented in Fig. 6. In the beginning of the experiment the wave Q_a could be appreciated as preceding the R_a, but it was so shallow and so little marked a phenomenon that its amplitude was indeterminable. However, after the injection of 100 mg. of procaine amide immediately above the head of the intracavitary electrode, the size of Q_a increases considerably so that its final amplitude at this stage is no less than 1.5 to 2 mm. It is also well to point out that artificial respiration during the inscription of both of these graphs was arrested, so that the position of the intracavitary electrode was maintained fairly constant.

DISCUSSION

In summarizing the results of our investigations, it could be stated that the initial negative deflection of the right auricular endoelectrogram has been found to possess the following characteristics.

1. It was a phenomenon which appeared in the graph derived from the upper part of the right atrium, generally at a relatively short distance from the region containing the main part of the S-A node.

2. This wave preceded Einthoven's "O" wave and practically coincided with the beginning of the totally negative deflections obtainable in the regions of the right atrium adjacent to the S-A node.

3. It was a right-auricular deflection, as could be inferred from the fact that the left-auricular complex, at least in the right-auricular endoelectrogram, was not preceded by a negative wave.

4. The size of the Q_a wave changed under the influence of the drugs which affect unfavorably the rate of the heart and the conduction of stimuli. The duration of the Q_a wave was affected only slightly. In contrast, the size of

this wave showed considerable change, increasing in the earlier and diminishing in the later phases of the heart muscle intoxication. In a stage of a very deep intoxication, and generally simultaneously with total arrest of the ventricles, one could sometimes see graphs in which the Q_a wave was prolonged or seemed to be separated from the principal body of the auricular complex.

It seems hard to believe that the hypothesis of Kossman and associates[19] covers all the facts which we have found during our investigation. If the exploring electrode at certain right-auricular levels were affected alternatively by a negative vector moving toward the lateral parts and a positive vector arriving through the septum, the stimulation of the left atrium would take place immediately after the upper part of the right atrium has barely been activated. This is, however, not the case as we know from earlier investigations of Luisada[24] and more recently from those of Franke and Gebert.[25] Also, we observed the entire left auricular complex following the end of the activation of the right auricle with an interval of time of about 0.02 sec. Moreover, if the negative initial deflection had the same origin as the positive wave which appears later, and both were inscribed on account of uneven distribution of potential, the amplitude of this negative deflection could not vary so much, and it could not be completely separated from the main auricular complex. On the other hand, the suggestion of Brown[10] and Battro and Bidoggia,[12] according to which the Q_a wave would be an independent S-A wave preceding the auricular complex, cannot be accepted, because according to modern electrocardiographic concepts, such a S-A node wave would be positive outside the sinus region. Moreover, such a sinus potential could probably be registered all around the S-A node and not in special spots at the upper level of the median parts of the right atrium. It should be remembered that in mammalians the sinus is closely incorporated in the wall of the right atrium. Its long axis, which was horizontal in the earlier stages of fetal development, becomes eventually vertical (Géraudel)[26] so that its right valve, the only one still identifiable, is represented by the crista terminalis. The sinus node itself is not a spherical or limited body, but an extensive horseshoe-shaped structure which embraces the ventral side of the termination of the superior vena cava and extends below the end of the upper half of the sulcus terminalis (Davies).[27] It is easy to understand, therefore, that the vectors accompanying the initiation of the stimulus in the head or (according to Prinzmetal and associates)[16] half-way between the head and the tail of the S-A node are not evenly distributed in respect to the body of the right atrium in the first stage of the accession. The site of the origin of the excitation will, of course, develop and maintain at this moment a negative potential. However, although there is a positive electrical potential in most parts of the right atrium, in isolated points close to the sinus node the resultant of all electromotive forces might well be slightly negative. This probably would occur particularly near the opening of two arms of the sinus node, and such a negative potential would be transmitted passively by the auricular muscle as far as it would be feasible under conditions of electrical conductivity, i.e., depending to a considerable degree on the direction of the long axis of the muscular fibers (Rothschuh).[28] In this way, the Q_a wave would

owe its existence to the negativity arising in the S-A node itself and spreading to a few parts on account of the electrical conductivity of the heart muscle (ionic, i.e., second class conductor). Such an explanation would include not only facts found during the present study, but other data as well. Thus, the synchronic beginning of the Q_a wave with the totally negative deflection generated in sites close to the sinus region is something to be expected. Also, we do not see any contradiction with the fact that, in favorable electrocardiographic leads, the P wave would be no more delayed than the Q_a wave of the endoelectrogram. It should be borne in mind that the Q_a wave is obtained through an unipolar lead and may not occur as early as the sinus wave obtained by means of two needles placed in the sinus region (Luisada).[29] On the other hand, in horses the Q_a wave should either precede or coincide with the so-called "O" wave of the limb leads. We have found the former to be true.

In respect to the general or local influence of drugs upon the size of the Q_a wave, the following can be said. The drugs used induced bradycardia and affected negatively the conduction of the stimuli. In late stages of intoxication, we observed occasionally an increase of the duration of the Q_a wave and, under extreme conditions, even its separation from the main auricular complex. However, the fact that under the influence of smaller quantities of drugs, the duration of the Q_a wave did not change seems to indicate that the main action of the drugs, at the beginning of the experiments, was effected through the alteration of the resting and consequently also acting membrane potential. We know that drugs reducing heart rate raise the membrane potential and vice versa. It is interesting to note that, in the course of our experiments, we observed an increase of magnitude of the Q_a wave in the earlier stages of digitalis intoxication, whereas the amplitude of the same wave diminished toward the end of the experiment. It should also be mentioned that this type of action might be exerted by influencing the so-called sodium pump (Keynes).[30]

In regard to the duration of the Q_a wave, it has been already mentioned that this was prolonged in the later phases of the experiments, i.e., at the moment when the amplitude of the deflection was decreasing and the signs of a marked intoxication of the heart muscle appeared. This might be interpreted as a result of a drop of the resting membrane potential together with a resistance to the spreading of the impulse. Our explanation could also possibly fit even the results of Sodi-Pallares'[15] experiments. The difficulty of assessing the absence of the Q_a wave from the higher endoauricular leads of a definite human or animal case is obvious. In order to be sure of such a situation one would have to explore with extreme detail the cavity of the upper third of the right atrium. If, in some cases, the initial negative deflection could be found in the lower right endoauricular leads, this could be due to the fact that in one particular spot the endoelectrode could be near the points connected with the sinoauricular node by a majority of longitudinal fibers, therefore, being in contact with suitable pathways for transmission of the stimuli as well as of electric currents.

SUMMARY AND CONCLUSIONS

1. The present experiments have been carried out on four horses, one mule, forty-three young bulls, and ten dogs. Various characteristics inherent to the inscription of the negative initial deflection in the right auricular endoelectrogram have been studied.

2. It has been estimated that judging by the length of the auriculoventricular conduction, the Q_a wave starts simultaneously with the totally negative auricular deflection which is typical for the sites adjacent to the S-A node and precedes the so-called "O" wave of the electrocardiograms of equines.

3. During the present investigation, the Q_a wave has been found only in the upper parts of the right atrium. It seems to be a purely right-auricular phenomenon, because it does not precede the left-auricular complex in the right-auricular endoelectrogram.

4. Drugs inducing bradycardia and slowing the conduction of the stimuli cause first changes of amplitude of the Q_a wave, then an increase of its duration and later its complete separation from the main auricular complex.

5. The Q_a wave can be considered the result of uneven distribution of vectors of electrical forces during the initiation of the stimulus by the S-A node and the preponderance of the negative forces in certain parts. This is thought to be the result of the nonspherical shape and the irregularity of structure of the S-A node.

SUMMARIO E CONCLUSIONES IN INTERLINGUA

1. Le negative deflexion initial del endoelectrogramma dexteroauricular (unda Q_a) esseva studiate in acute experimentos con 4 cavallos, 1 mulo, 43 tauros, e 10 canes.

2. Le unda Q_a coincideva con le totalmente negative deflexion auricular que es typic con sitos adjacente al nodo sinoauricular e precedeva le si-appellate unda O del electrocardiogramma equin; illo esseva observate solo in le parte superior del atrio dextere; illo non precedeva le complexo sinistroauricular in omne casos ubi iste complexo appareva in le endoelectrogramma dexteroauricular.

3. Drogas que induce bradycardia e retardation de conduction comenciava per producer cambiamentos del amplitude del unda Q_a; tunc illos causava un augmento del duration de ille unda; e finalmente illos produceva su separation ab le complexo auricular principal.

4. Le unda Q_a poteva depender del preponderantia del fortias electric negative in alicun punctos proxime al nodo sinoauricular como resultato de su forma non-spheric e su structura irregular.

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EXPERIENCES WITH THE RUDIMENTARY ANTERIOR WALL INFARCTION

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TWELVE years ago I called attention to a clinicoelectrocardiographic syndrome under the name of "rudimentary anterior wall infarction." Clinically this syndrome is characterized by the onset of severe attacks of angina pectoris which are not unduly prolonged as in status anginosus, normal temperature, leukocytes, and sedimentation rate. Electrocardiographically (Fig. 1) the QRS complex is not altered, but the RS-T segment and T wave exhibit changes in the same leads as are seen during the evolution of an anteroseptal wall infarction. As in many of these latter cases the isolated monophasic deformation phase is absent in the earliest stages of the infarction. Instead the first electrocardiographic change is the intermediate stage characterized by RS-T segment elevation and sharply pointed terminally inverted T waves. This pattern and later the isolated invertedly pointed T waves are most pronounced in the region between the left sternal border and the apex. Corresponding changes may be absent in the limb leads or may be barely apparent in Lead I.

In my first paper I collected several cases with an acute onset of the anginal attacks and with the development of the mentioned electrocardiographic alterations in the same time.[2] Therefore, the conclusion seemed justified that this clinicoelectrocardiographic picture could appear as an acute morbid episode and, furthermore, that the anatomic basis might be a small or scattered infarction in the left anterior ventricular wall produced by the obstruction or severe narrowing of a small branch of a coronary artery. Follow-up studies of these cases revealed that some were completely free from any cardiac disturbances and had a normal tolerance to effort. In these instances it was concluded that there were not any other branches of the coronary arteries which were narrowed. However, in other individuals simple anginal attacks on effort and the ischemic stage of the electrocardiogram persisted. This may indicate that there was a more diffuse involvement of the coronary artery system. Post-mortem studies are not available except in isolated instances because of the relatively benign nature of the process. The latter is due in part to the small size of myocardium involved. The prognosis of this syndrome is favorable.[3]

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Similar electrocardiographic changes have been confirmed by apposite scars in a case dying of intercurrent infection (East and Oram)[4] and lately in another instance complicated by ventricular hypertrophy (Jedlicka).[5] Also Burger and associates[1] were successful in producing the same electrocardiographic changes experimentally by appropriately located myocardial lesions.

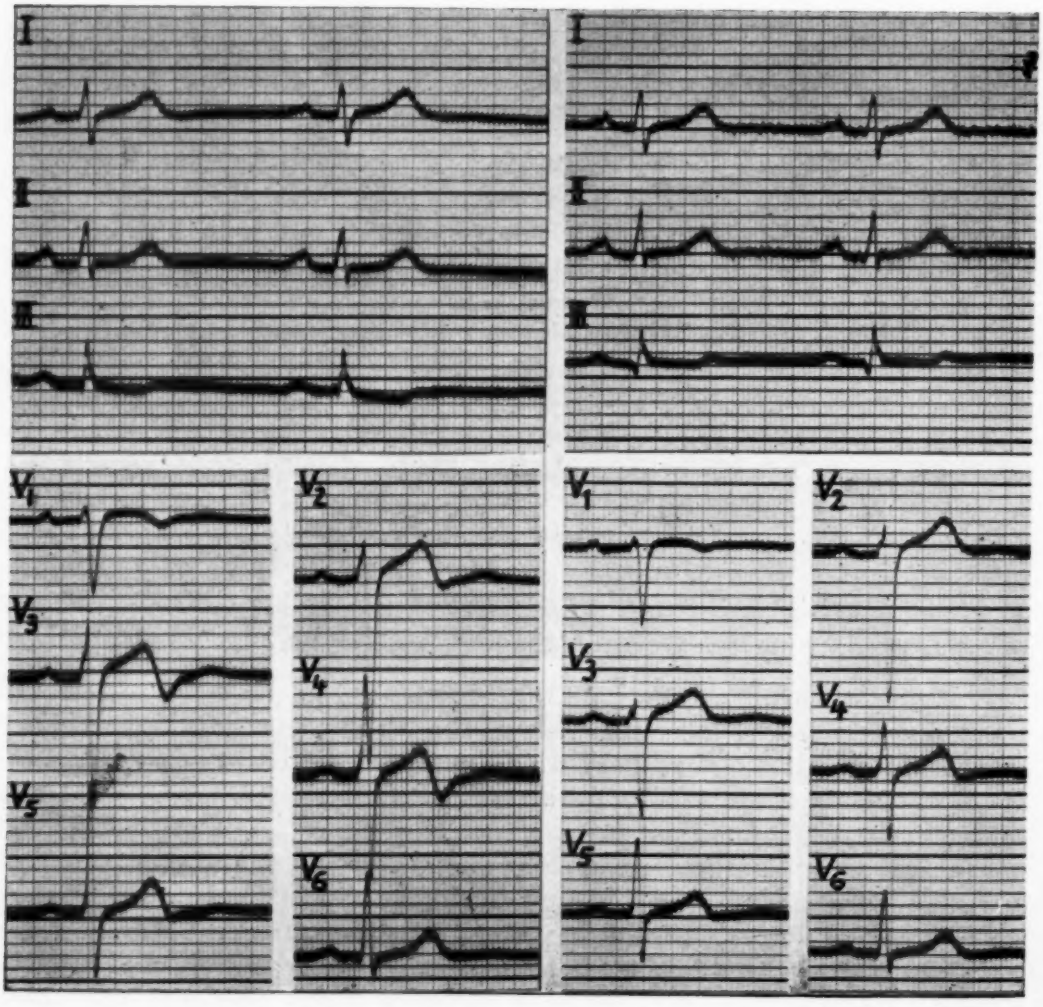

Fig. 1.—Rudimentary anterior wall infarction in a 40-year-old man. Standard leads. *A*, Dec. 1, 1951. After 20 days of angina pectoris gravis acuta. *B*, Jan. 31, 1952. Almost complete restitution 2 months later.

A typical case is represented by B.H., a 46-year-old businessman who was free from any previous or family history of cardiovascular disease. His social habits were not remarkable other than that he smoked twenty cigarettes per day. He began to develop angina pectoris on walking, April 1, 1939. These attacks became more frequent and increased in severity over a three-week interval. He consulted another physician who recommended nitroglycerine which afforded him marked relief.

I first examined him on April 22, 1939, and at that time his blood pressure was 145/100 mm. Hg; white blood count 6,280; sedimentation rate 5/11 mm., and the chest roentgenogram was normal. The electrocardiogram revealed a sinus rhythm with a P-R interval of 0.18 sec. The QRS complex was normal. The T wave was diphasic (plus-minus) in Leads I and V_2 through V_5. The sharply terminally inverted T wave was maximum in Lead V_3. The Q-T interval was normal for the rate.

During the next two weeks, with restricted activity, the anginal attacks decreased and the T-wave inversion became less. One month after the first electrocardiogram (May 20, 1939) the T waves in all standard leads were upright, and two weeks later the anginal attacks completely disappeared. He was examined four years later (Jan. 14, 1943) and had been completely free from angina pectoris. Physical and fluoroscopic examinations were normal. The electrocardiogram was completely normal both at rest and after an exercise test (climbing ten floors). He was next seen thirteen years after his initial episode (April 8, 1952) and he was asymptomatic. His walking capacity was normal.

In the past twelve years I have been able to collect and observe both clinically and electrocardiographically eighty cases of this syndrome.

An investigation of the electrocardiographic pattern has to take into consideration that it is representative of only the localization of the injury but not of the etiology. Therefore, similar tracings may be caused by myocardial inflammation of any origin which is chiefly focal in character. The evaluation of the electrocardiographic pattern is only possible in conjunction with the clinical data. In a number of cases the T-wave inversion persisted for a much longer period than a few weeks or months, and in one case lasted for over a year. All of these cases concerned elderly individuals or those with left ventricular hypertrophy. Occasionally the U wave was inverted in the same leads as the T wave and the two were partially merged. In one case the typical T pattern was temporarily abolished by the appearance of a left bundle branch block. More detailed electrocardiographic exploration of the chest (Fig. 2) disclosed that the T-wave abnormalities sometimes appeared only in Leads V_{2-4}. Whenever the chest lead system of Nehb was used, it was always Leads A and J which depicted the T-wave inversion.

During the last year I had the opportunity to examine some cases by vectorcardiography. It was to be expected that a system which employs electrodes at a distance from the heart and without using the precordium would not be of great value (Fig. 3). Indeed the results were very poor in that they revealed an almost indistinguishable abnormality of the T loop. They contrasted with the generally striking changes in the chest leads and confirmed the experience that this method is not appropriate to disclose small lesions in the anterior wall of the left ventricle.

Clinically the syndrome was not always solely characterized by an acute onset of frequent simple anginal attacks of the ambulatory type. Occasionally these attacks were replaced by an anginal state. Frequently, however, the syndrome was related to a special type of angina pectoris which might be called angina pectoris gravis (acuta). This occurs not only on effort but sometimes at rest, occasionally lasts longer than ten minutes, and is not always promptly relieved by nitroglycerine. As a rule these clinical manifestations are not accompanied by the described electrocardiographic pattern. In other instances there may be the picture of RS-T depression in most of the standard leads with-

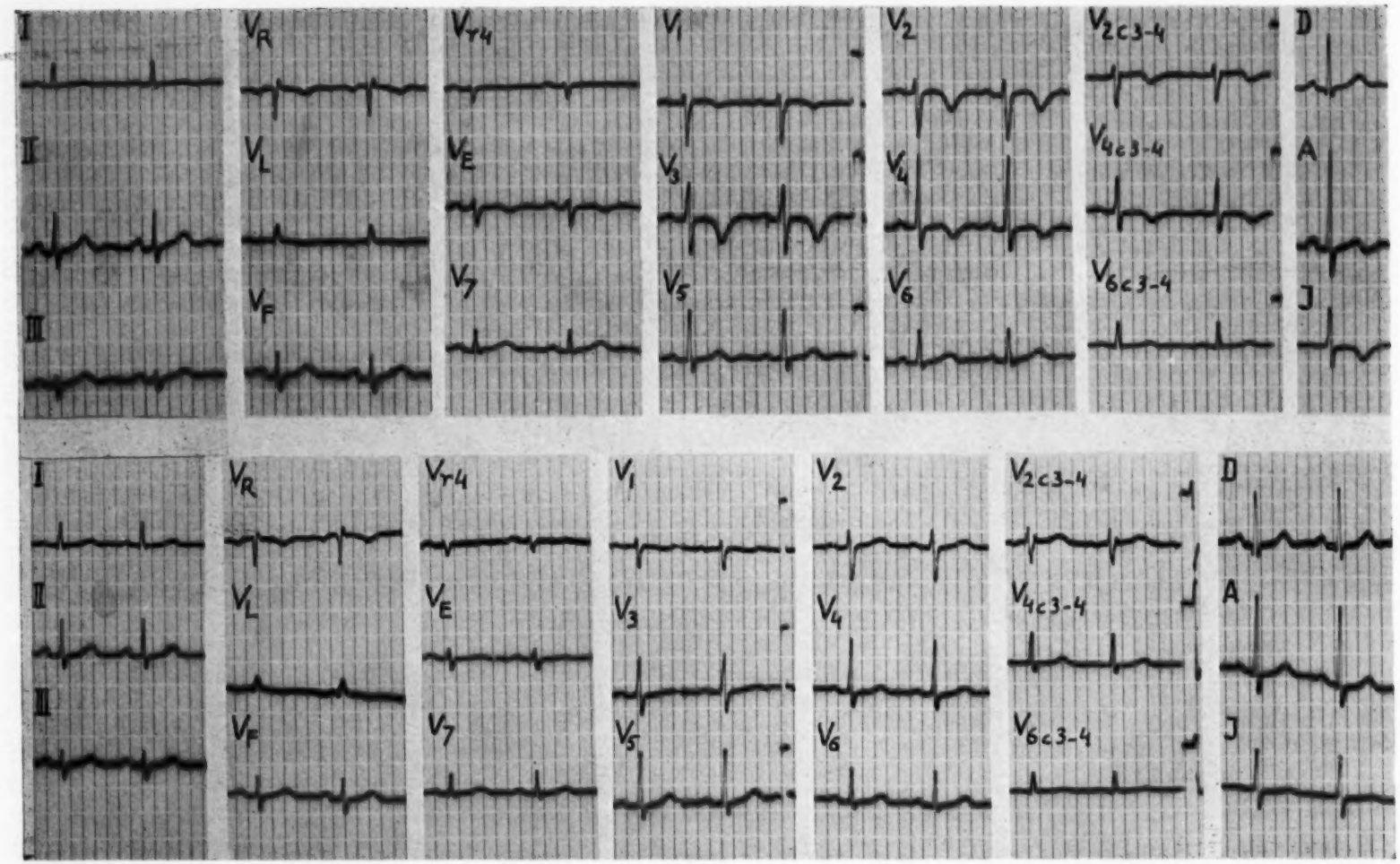

Fig. 2.—Rudimentary anterior wall infarction in a 55-year-old woman. Electrocardiographic exploration. *A*, Dec. 22, 1953. After 12 days of angina pectoris acuta gravis; *B*, Feb. 15, 1954. Almost complete restitution 7½ weeks later.

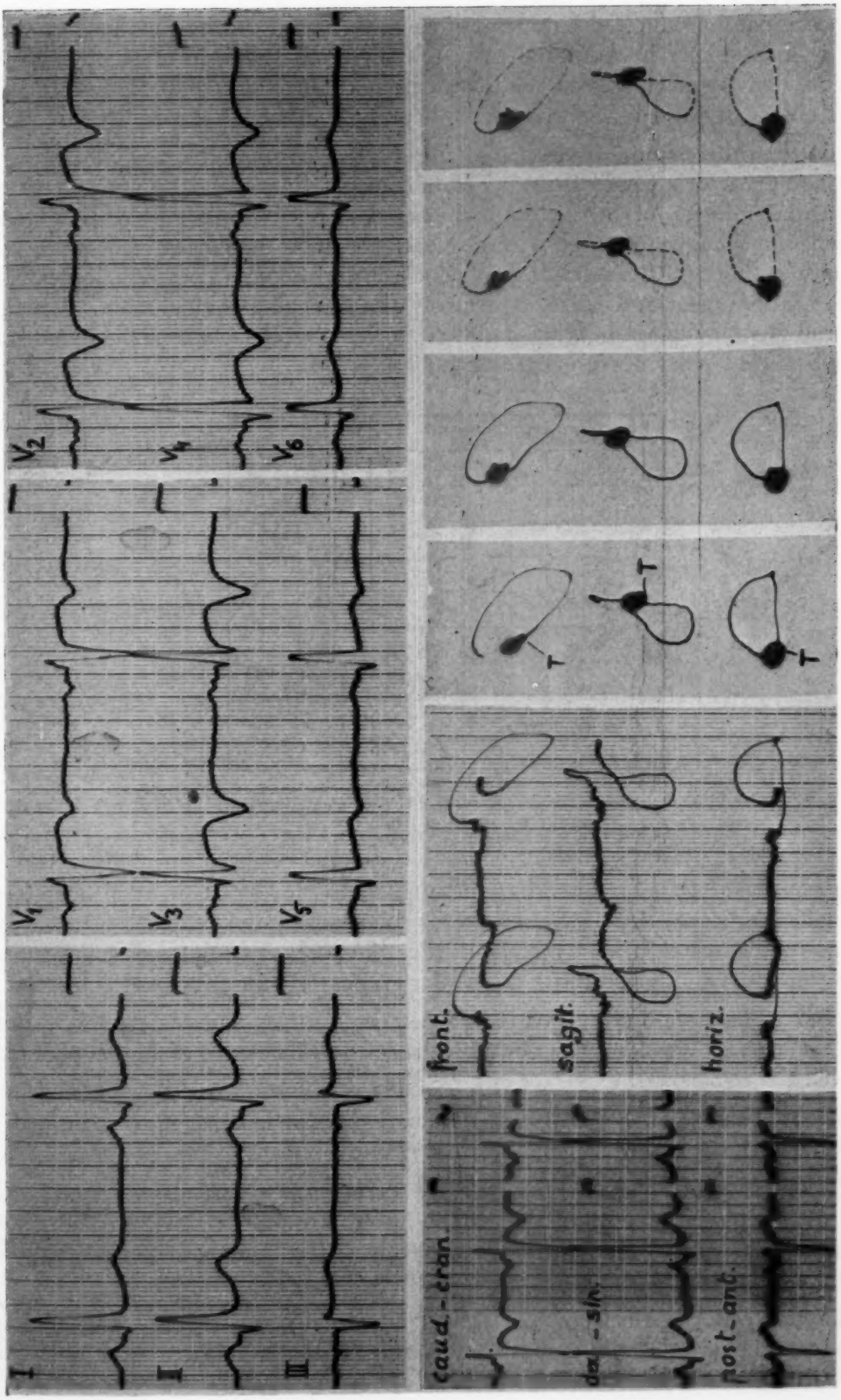

Fig. 3.—Rudimentary anterior wall infarction in a man of 61 years of age. Typical T-wave inversion in leads V_2-V_4. In contradistinction the vectorcardiogram in three planes (Duchosal method) yields a normal position of the T loop.

out accompanying anginal pain, but it is accentuated during anginal attacks. This is most likely attributable to a prolonged coronary insufficiency. One can consider this pattern as a prodromal stage of an infarct, but this evolution is not obligatory and it can pass without any apparent myocardial lesion.

On the other hand I investigated the cases of accumulated angina pectoris and angina pectoris gravis in order to find out if they could be attributed to myocardial injuries of other localizations. We must assume that this may happen, but it appears to be a rare event. In most instances of T-wave inversions (without QRS alterations) in association with angina pectoris, indicative of a lateral or posterior localization, there was a foregoing anginal state. Therefore, rudimentary anterior wall infarction merits a special place in the diagnosis of the natural history of coronary artery disease.

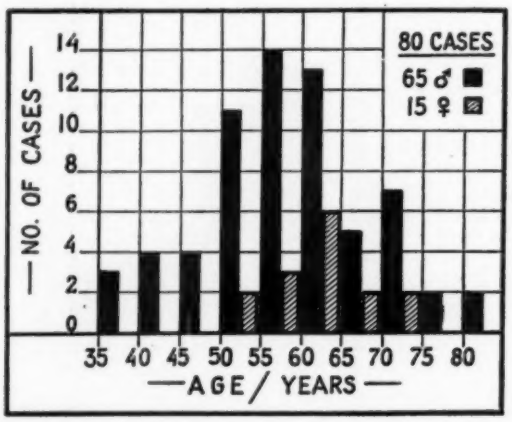

Fig. 4.—Clinical and electrocardiographic course of 80 cases of rudimentary anterior wall infarction with a follow-up of 1 to 15 years.

Frequency: It is obvious that these cases are not as frequent in hospitals as in office practice. Among the various manifestations of angina pectoris in the last 450 cases seen in my office during the past three and one-half years, there were forty (8.9 per cent) cases of rudimentary anterior wall infarction.

Sex: There were sixty-five (81.25 per cent) males and fifteen (18.75 per cent) females. This closely agrees with the over-all incidence of angina pectoris between the two sexes.

Age: The age of the eighty subjects varied between thirty-five and ninety-one years with the majority being between fifty to sixty-five years of age (Fig. 4).

The relationship of the syndrome in the development of coronary artery disease (Fig. 5): In twelve patients the angina pectoris and the attributed electrocardiographic pattern disappeared completely. The follow-up period in this group was from one to fifteen years.

In thirteen the electrocardiographic pattern disappeared but the angina pectoris persisted in a mild ambulatory form. These individuals were followed for twelve years.

In eight there was a regression of the clinical and electrocardiographic signs, but this group did not have an adequate follow-up period.

Following improvement, two patients developed anginal states with extensive myocardial infarcts. They later made complete clinical and electrocardiographic recovery. However, in two other patients there followed, after extensive infarction, angina pectoris simplex which terminated in sudden death. Two additional patients could not be followed.

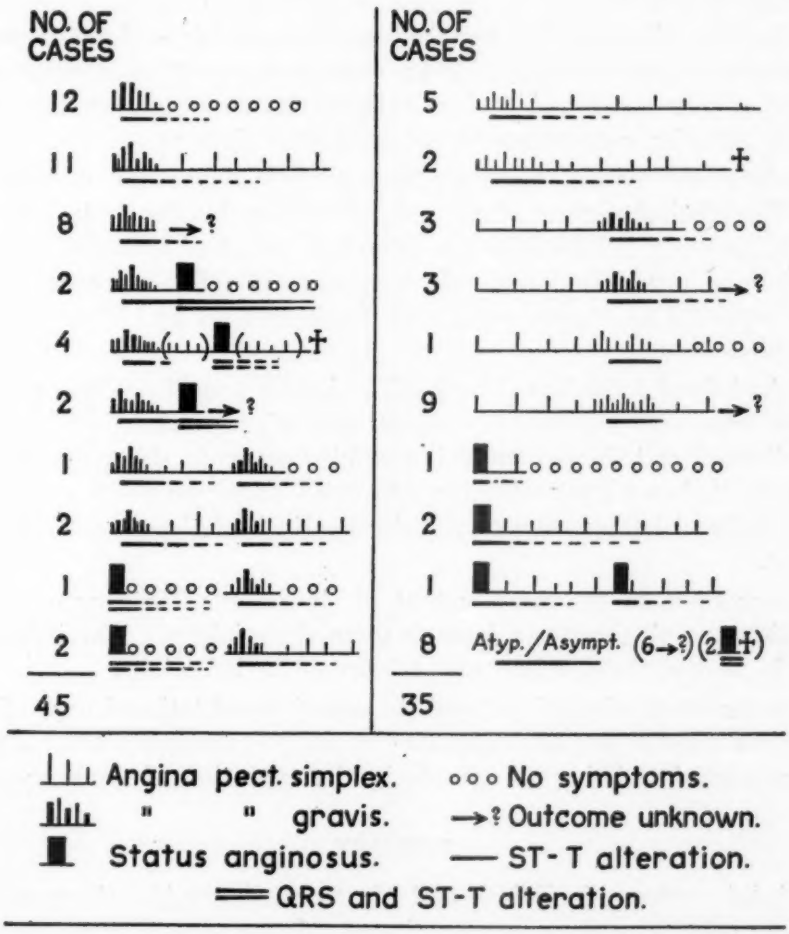

Fig. 5.—Age and sex distribution of 80 cases of rudimentary anterior wall infarction.

Three had repeated rudimentary anterior wall infarctions within six months to two and one-half years of their first attack. One of these became clinically cured, and the other two had angina simplex.

In two the angina pectoris gravis acuta with rudimentary anterior wall infarction was not the initial symptom but was preceded by an extensive infarct followed by an asymptomatic interval of eight months to two years.

Seven were characterized clinically only by the acute onset of recurrent attacks of angina pectoris simplex. After the disappearance of the electro-

cardiographic pattern, similar attacks rarely persisted. Death occurred in two of these seven cases.

In sixteen (six with angina pectoris gravis and ten with accumulated angina pectoris simplex) rudimentary anterior wall infarction was not the beginning of their coronary artery history but was preceded by a period of angina pectoris simplex lasting several months to three years. Nevertheless, four remained asymptomatic after their attack and the remaining twelve did not have a satisfactory follow-up period.

Four electrocardiographically typical cases were initiated by a longer lasting angina pectoris which we must call an anginal state. One became clinically cured. The others continued to have angina pectoris simplex, but in one a rudimentary anterior wall infarction recurred after eight years.

Eight had the typical electrocardiographic pattern but without angina pectoris. The clinical picture of generalized arteriosclerosis made it likely that the same underlying mechanism was present: one had dyspnea equivalents, one, 79 years of age, was completely asymptomatic, two were asymptomatic but later developed an anginal state and death, and six had hypertension with cardiac failure.

Eight had focal infections (three with chronic tonsillitis, two with dental granulomas, one with chronic bronchitis, one with prostatitis and one with Buerger's disease) and the electrocardiographic pattern in this group was probably due to an inflammatory etiology. Four of these were followed and were cured of their local inflammatory conditions. Each of these made an uneventful recovery.

In consequence of the small extent of the lesions the prognosis is good. However, the over-all prognosis depends upon the etiology. The inflammatory cases had the best outcome subsequent to cure of the infections.

The treatment consists of rest and the use of vasodilating drugs. Complete bed rest is not needed and anticoagulant therapy is advisable only if this syndrome is suspected of being an episode in the evolution of coronary sclerosis.

SUMMARY

This brief review of clinical and electrocardiographic characteristics of rudimentary anterior wall infarction, based on the study of eighty cases, is presented to make known better a not infrequent clinicoelectrocardiographic syndrome.

Its relation to angina pectoris gravis acuta, the differential diagnosis of the clinical syndrome and of the electrocardiographic pattern are discussed. In the vectorcardiogram T-wave abnormalities may be lacking.

The natural history of the eighty cases and their evolution among the different forms of coronary artery disease is reviewed.

Some atypical cases are separately discussed.

The nature of the anatomic pathologic lesion is considered, but due to the good prognosis of the syndrome personal post-mortem findings are lacking.

SUMMARIO IN INTERLINGUA

Iste breve revista del characteristicas clinic e electrocardiographic del infarcimento rudimentari del pariete anterior es basate super un studio de 80 casos. Illo es presentate pro propagar le familiaritate con iste non infrequente syndrome clinicoelectrocardiographic.

Es discutite le relation de infarcimento rudimentari del pariete anterior con grave angina acute de pectore e etiam le diagnose differential del syndrome clinic e del configuration electrocardiographic. In le vectocardiogramma anormalitates del unda T pote esser absente.

Le historia natural del 80 casos e lor evolution inter le differente formas de morbo del arteria coronari es revidite.

Es presentate un discussion separate de alicun casos atypic.

Le natura del lesion es considerate ab le puncto de vista anatomicopathologic, sed proque le prognose del syndrome es generalmente bon, le autor non dispone de ulle observationes post morte in su experientia personal.

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THE BALLISTOCARDIOGRAM OF THE NORMAL DOG

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THE purpose of the present study is to present the technique, normal configuration, and time relationships of the dog ballistocardiogram, before and after opening the thoracic cage. In addition, the similarity to the human ballistocardiogram will be discussed.

TECHNIQUES

The dog was placed supine in a sand box and partially buried in the sand, with sandbags on both sides of the shoulders and head for stabilization. The dog's head was secured in a slightly flexed position by means of a string attached to each side of the sand box so that the vertebral column formed a straight line. A bellows pickup, similar to that described for recording human ballistocardiograms,[1] was placed against the lambdoid region of the head of the dog at a pressure of 5 mm. Hg. A Cambridge piezoelectric transducer was connected to the bellows, and output was recorded on a Sanborn four-channel direct-writing Poly-Viso instrument. The bellows and transducer were compactly mounted on a weighted stand adjustable in height, with a mechanical ram to hold the bellows in place against the dog's head at the desired pressure. Records were made with the sand box and apparatus on a solid floor, as any type of table mount tried introduced artifacts due to table vibrations. By the use of this technique, reproducibility of the ballistocardiogram could be obtained from day to day in the same dog.

Electrocardiogram, phonocardiogram, ballistocardiogram, and carotid-jugular pulses were recorded simultaneously. Lead II electrocardiogram was usually employed as a reference for timing purposes because of the prominence of the P and QRS complexes. The carotid-jugular pulse was recorded by means of a gelatin capsule placed against the neck of the dog. In later experiments a Sanborn Electromanometer with a polyethylene catheter inserted through the carotid artery into the aortic arch was used to obtain an aortic pressure pulse. Heart sounds were recorded with the standard Sanborn Microphone.

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It was necessary to slow the heart rate of the dog to 70 to 120 beats per minute in order to prevent the diastolic ballistic waves from being obscured in the subsequent systolic waves. It was found that two grains (120 mg.) of morphine sulfate injected subcutaneously one hour prior to recording served to produce an adequate slowing of the heart rate. Other methods of inducing bradycardia, such as faradic stimulation of the intact right vagus nerve and esophageal cooling of the sinoauricular node, were also investigated but proved less desirable. Hypothermia was used in conjunction with morphine sulfate in later experiments. The effects of hypothermia will be presented elsewhere. Nembutal sodium, 30 mg. / kg. of body weight, was given intravenously just prior to recording.

Artificial respiration was administered routinely with a Bird respirator pump in which the stroke volume and rate could be varied to produce any desired degree of ventilation. The respirator was connected to an intratracheal cannula by a short length of rubber tubing. In a dog weighing 12 kg. a stroke volume of 500 mm. with a rate of 20 strokes per minute produced adequate ventilation and prevented respiratory attempts on the part of the dog during the recording period of about 45 seconds while the respirator was stopped. It was deemed more advisable to inhibit respiratory attempts by mild hyperventilation rather than by administration of respiratory paralytic drugs such as succinylcholine or tubocurarine. It was found that the degree of hyperventilation thus produced did not alter the ballistocardiogram.

The thorax was opened by means of a midsternal incision from the level of the second rib to the xiphoid process. After the chest was opened and retracted, the internal mammary vessels were isolated and ligated. The amount of blood loss during the operation was minimal.

Records were made on twenty-three normal dogs, and were repeated twice on five of the animals, giving a total of thirty-three observations. Studies were made immediately before and again after opening the chest in twelve dogs.

RESULTS

Time Relationships of the Dog Ballistocardiogram With Chest Closed.—Table I presents the range and mean values of the time relationships observed in the ballistocardiographic waves taken on normal dogs. The mean values from human studies by this type of technique are also included for reference.[2] In rare instances it is difficult to obtain consistent ballistocardiograms in very small dogs. Fig. 1 presents simultaneous traces of the ballistocardiogram, heart sounds, aortic pressure pulse, and electrocardiogram. There are several significant differences in the time relationship as recorded in the dog ballistocardiogram from that in human beings. The period of ejection is much shorter in the dog than in human subjects. In addition, the first sound tends to occur 0.02 sec. earlier in the dog than in human beings. The time of the G point of the ballistocardiogram from the onset of the QRS complex is similar in dogs and in human beings; however, the I point tends to occur earlier, and the durations of the H-I and I-K periods are shorter in dogs than in human subjects. In most

TABLE I

CYCLE	DOG BCG WITH CHEST CLOSED				DOG BCG WITH CHEST OPEN				HUMAN MEAN (SEC.)
	NUMBER OF OBSERVATIONS	RANGE (SEC.)		MEAN	NUMBER OF OBSERVATIONS	RANGE (SEC.)		MEAN (SEC.)	
		MAXIMUM	MINIMUM			MAXIMUM	MINIMUM		
R-R	32	1.60	0.28	0.805	12	1.92	0.26	0.581	0.08
P-R	32	0.22	0.07	0.136	12	0.16	0.10	0.116	0.16
Q-S_1	16	0.05	0.00	0.032	—	——	——	——	0.043
Q to Ce	23	0.12	0.08	0.093	11	0.16	0.06	0.113	0.12
Q-G	32	0.10	0.02	0.053	12	0.10	0.02	0.039	0.044
Q-H	32	0.16	0.04	0.088	12	0.12	0.05	0.071	0.085
Q-I	32	0.18	0.08	0.112	12	0.14	0.08	0.104	0.144
S_1-G	16	0.06	−0.02	0.016	—	——	——	——	0.007
S_1-H	16	0.08	0.01	0.046	—	——	——	——	0.044
H-Ce	24	0.04	0.00	0.014	11	0.06	0.00	0.039	0.034
Ce-I	24	0.02	0.00	0.012	11	0.04	0.01	−0.009	0.026
G-H	32	0.04	0.01	0.026	12	0.07	0.02	0.033	0.04
H-I	32	0.05	0.01	0.027	12	0.05	0.02	0.031	0.06
K-S_2	16	0.08	0.00	0.040	—	——	——	——	0.02
L-Cin	23	0.02	0.00	0.001	5	0.10	−0.02	0.032	0.01
H-K	23	0.24	0.08	0.123	12	0.18	0.08	0.138	0.24
I-K	30	0.18	0.05	0.097	12	0.15	0.06	0.106	0.18
Q-K	30	0.25	0.16	0.205	10	0.16	0.06	0.188	0.32
Q-Cin	23	0.36	0.18	0.280	12	0.25	0.17	0.224	0.39
S_2-L	11	0.03	0.01	0.026	—	——	——	——	——

Ce = carotid or aortic ejection; Cin = carotid incisural notch or aortic incisural notch; S_1, S_2 = first and second heart sounds; G-H-I-J-K-L refer to points rather than waves.

instances there is a sharp headward movement in late systole ending at the carotid incisural notch, or at the time of the L point in the human ballistocardiogram (Fig. 1).[2] Thus it appears that the L point as labeled in Fig. 1 is comparable in the dog and human ballistocardiograms. Assuming this to be true and that the K is the first footward movement following the J peak, then there usually occurs in the dog an extra headward and footward sequence between the K and L points (Fig. 1). A notched K-L upstroke is sometimes seen in normal

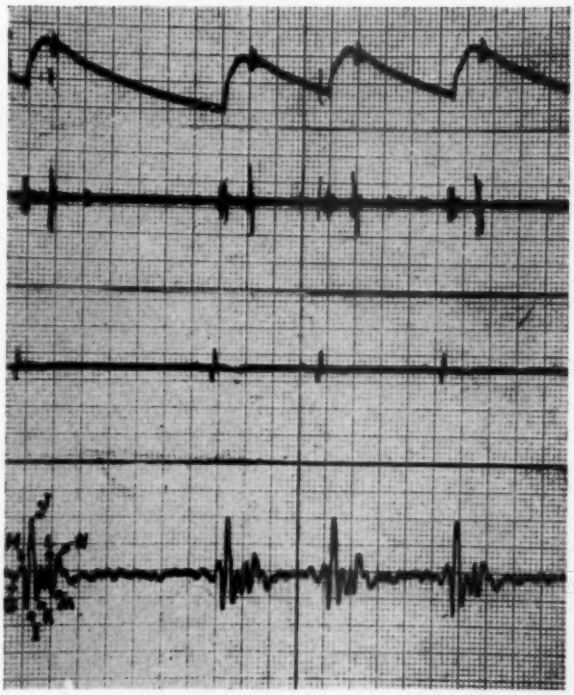

Fig. 1.—This is a tracing of a representative ballistocardiogram (*D*) taken from the dog with simultaneously recorded aortic pressure pulse (*A*), heart sounds (*B*), and a Lead II electrocardiogram (*C*). Note that the general configuration of the ballistocardiogram is similar to that of the human, with a well-defined G-H-I-J-K sequence. The G-H upstroke begins well after the onset of the QRS complex and is presumed to be due to ventricular forces. The H-I and I-J movements are not too dissimilar from those noted in human tracings. One significant difference in the tracing presented from that usually noted in the human ballistocardiogram is the appearance of an extra headward-footward movement occurring in late systole before the incisural notch. This extra movement is apparently interpolated between the K and L points. The L-M sequence is labeled and corresponds in time to that of the human ballistocardiogram and resembles it in configuration. This adds evidence that the late systolic movement is a true extra movement.

human subjects. Occasionally this movement is represented only by a notch in the J-K downstroke when the heart rates were exceptionally fast. The presence of this extra wave is the most consistently different feature of the dog ballistocardiogram from that usually noted in the human being. Further evidence that is is a true extra wave in the ballistocardiogram is obtained by studies following hypothermia in the dog, in which there is a marked prolongation of systole as a result of cooling. The late extrasystolic wave becomes quite distinct, prolonged in duration, and is followed by the sharp headward movement ending at the L point at the time of the carotid incisural notch.[3]

Ce — carotid or aortic ejection; Cin — carotid incisural notch or aortic incisural notch; S_1, S_2 = first and second heart sounds; G-H-I-J-K-L refer to points rather than waves.

In summary, the G and H waves in the dog and human ballistocardiograms bear similar relationships to the electrocardiogram. The I-J-K sequence in the dog is briefer in duration, apparently as the result of the shortened systole.

Configuration of the Dog Ballistocardiogram With Chest Closed.—Fig. 2 illustrates representative types of ballistocardiograms obtained from several dogs. In Fig. 2,*A* it is easily noted that the configuration of the ballistocardiogram is similar to that in human subjects; however, there appears a small extra movement following the K point. Note that the G-H upstroke begins well after the onset of the QRS complex and therefore is probably a "true" ventricular

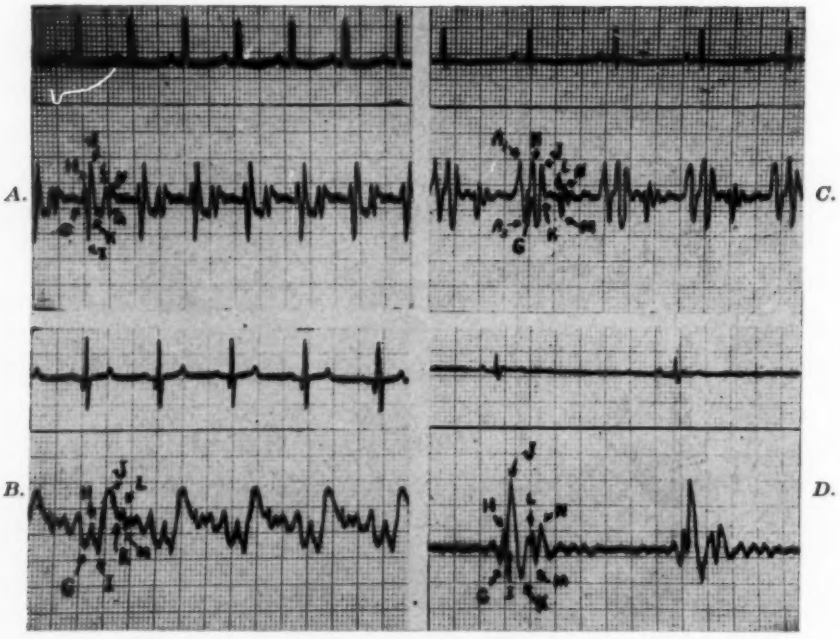

Fig. 2.—This presents the ballistocardiogram and simultaneous electrocardiogram from four dogs with closed chests, to illustrate some of the variations in patterns observed. Note that in Dog *A* the late extrasystolic movement is represented by a small headward-footward notch in the trace. In Dog *B* the movements following the P wave and before the onset of the QRS complex are noted to be somewhat large and presumed to be due to auricular activity. The relative height of the K point is quite variable and in this dog the take-off is quite high. In this particular ballistocardiogram the late extrasystolic movement is not noted. In Dog *C* the movements following the P wave and before the QRS complex are again noted to be quite large and of equal amplitude to that noted for the H-I and I-J movements. In addition the G-H upstroke begins after the notch in the previous headward auricular movement, probably as a result of ventricular activity. The H-I downstroke again is quite prominent in this particular dog, with a relatively small I-J upstroke. Again a well-defined late extrasystolic movement is noted occurring before the L point in the ballistocardiogram. Note the sharp L-M downstroke. In Dog *D* the H-I downstroke is relatively small in comparison to the I-J upstroke.

force. In Fig. 2,*B* there are rather pronounced movements, probably auricular in origin, which begin following the P wave in the electrocardiogram and extend to approximately 0.04 sec. after the onset of the QRS complex, or up to the G point. The H-I downstroke, as noted in this particular dog, is not exceptionally deep. The K wave is often variable in respect to its depth. In Fig. 2,*B* the K point is high while in Fig. 2,*D* the K point is deep and below that of the I point. In Fig. 2,*C* the auricular movements in the ballistocardiogram are

approximately the same size as that of the H-I-J sequence. In this instance the H-I downstroke is deep while the I-J upstroke is relatively small. In Fig. 2,*D* the H-I downstroke is small in comparison to the other ballistic waves with the presence of a prominent I-J upstroke. The L-M downstroke is usually abrupt and distinct in most dogs. In general, it is reasonable to say that the configurations of the dog and human ballistocardiograms are similar; however, there are some alterations in the relative amplitudes of the various movements. The dog ballistocardiogram does appear to have a distinct late extrasystolic headward and footward movement after the K point, terminating before the L point or the carotid incisural notch.

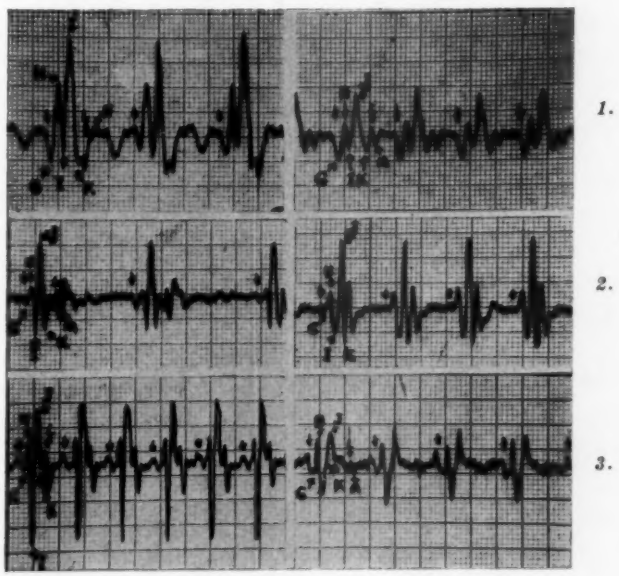

Fig. 3.—This presents tracings from three dogs before (*A*) and after (*B*) opening the thoracic cage. The arrow before each complex indicates the onset of the QRS. Note the minor differences in both amplitude and configuration; however, the time relationships and the basic pattern of the G-H-I-J-K sequence are preserved after opening the chest cage.

Time Relationships of the Dog Ballistocardiogram With Open Chest.—Satisfactory ballistocardiograms are usually obtained following the opening of the chest. In general, small dogs are more likely to have unsatisfactory ballistocardiograms. In a few instances there is no apparent reason for unsatisfactory tracings. Occasionally the ballistocardiogram is poor just after opening the chest but becomes satisfactory after a brief period of time elapses.

Table I presents the time relationships of the ballistocardiogram obtained after opening the thoracic cage in the dog. Note that in general the time relationships are quite similar to those obtained with the chest closed. Some of the small differences observed are possibly due to the increased heart rate following the surgical manipulation. Although the time of the various points in relationship to the QRS complex and duration of movements is similar in tracings obtained with the chest open and with the chest closed, the tracings with the open chest often lose the usual relationships to the carotid or aortic

pressure pulse. In some instances ejection apparently begins at the I point rather than shortly after the onset of the H-I downstroke. In addition, the L point does not bear as close relationship to the carotid or aortic incisural notch. However, it seems reasonable that the ballistocardiogram obtained with the chest open may be used in studying the genesis of the various ballistic waves.

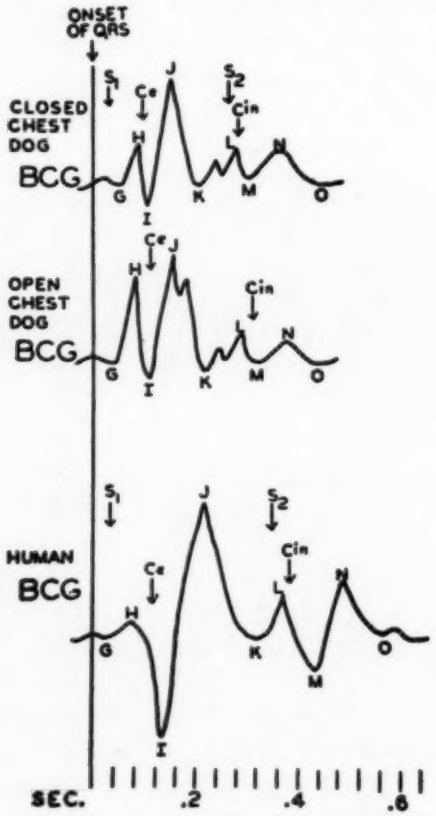

Fig. 4.—This is a composite drawing of a representative ballistocardiogram from the dog before and after opening the thoracic cage. A typical human tracing obtained by similar technique is presented for comparison. Ce indicates the onset of the carotid upstroke and Cin the carotid or aortic incisural notch. S_1 and S_2 refer to the first and second heart sounds. Note that the major differences between the dog and human ballistocardiogram are probably the result of the short systolic period with the compression of the G-H-I-J-K sequence into a shorter period of time. The basic pattern and time relationships of the dog ballistocardiogram before and after opening of the chest appear comparable in most ways to the human ballistocardiogram.

Changes in Configuration of the Dog Ballistocardiogram With the Chest Open.—There are several minor changes noted in the configuration of the ballistocardiogram following the surgical opening of the thoracic cage. Fig. 3 presents the ballistocardiograms before and after opening the chest in three dogs. Occasionally the auricular movements and G-H upstroke become more prominent following the surgical procedure. The I-J-K sequence often develops a notch; however, the late systolic and diastolic sequences of the ballistocardiogram were rarely significantly altered.

Fig. 4 presents composite drawings of the dog ballistocardiogram both with the chest open and the chest closed, and the human ballistocardiogram for comparison. The differences between the human and dog ballistocardiograms

may be explained by the shortened systolic period in the dog which compresses the movements into a shorter period of time.

COMMENTS

This study demonstrates a technique by which dog ballistocardiograms can be obtained in the closed and the open chest. As the configuration and time relationships of the ballistocardiograms are only slightly altered following opening of the chest, it is reasonably assumed that the dog ballistocardiogram may be used in the study of the genesis of the various movements. This assumption is probably more reasonable if control tracings are obtained just preceding and following acute experiments. Studies along this line will be presented in future publications.

SUMMARY AND CONCLUSIONS

1. A reliable and reproducible technique in recording the dog ballistocardiogram is presented.

2. The time relationships of the ballistocardiograms in dogs with closed and with open chests to the heart sounds, carotid and aortic pressure pulses, and electrocardiogram are presented.

3. Opening the thoracic cage does not appreciably alter the time relationships of the ballistocardiogram; however, some differences in the configuration do occur.

4. In general, the configurations of the dog and human ballistocardiograms are similar, the only noticeable difference being a late extrasystolic headward and footward movement between the K and the L points in the dog ballistocardiogram.

5. This study indicates that the dog may be used in more direct investigations of the genesis of the various ballistocardiographic waves.

SUMMARIO IN INTERLINGUA

Es describite un methodo pro prender directe ballistocardiogrammas displaciamental in canes tanto a thorace aperite como etiam a thorace claudite.

Es presentate un studio del relation temporal del undas ballistocardiographic in canes a thorace aperite e claudite con sonos cardiac, pulsos de pression carotide e aortic, e electrocardiogrammas. Esseva constatate que ballistocardiogrammas de canes e de humanos es simile, si illos es prendite per methodos analoge, excepte que in le caso del can le systole es plus breve e le intervallo ab le puncto K al puncto L es characterisate per le apparition de un movimento extrasystolic tardive verso le capite e le pedes. Nostre successo in prender satisfacente ballistocardiogrammas ab canes a thorace aperite indica que le can pote esser usate in additional investigationes directe del genese del varie undas ballistocardiographic.

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THE EFFECTS OF OCCLUSION OF THE VENAE CAVAE, AORTA, AND PULMONARY ARTERY ON THE DOG BALLISTOCARDIOGRAM

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THE problem of the genesis of the individual waves of the ballistocardiogram has been approached by various methods. The original studies of Starr and associates[1] were based upon the application of Newton's third law of motion which states that, " . . . for every action there is an equal and opposite reaction." They correlated the curve of the force of cardiac ejection with the ballistocardiogram. An acceleration factor which was derived from the velocity of blood in the dog aorta as determined by Machella[2] was used in calculating the force of cardiac ejection. Hamilton and associates[3] also correlated the ballistocardiographic pattern with the force of cardiac ejection using the pressure pulse contour method of deriving an ejection curve. Starr and associates[4] have subsequently compared the third derivative of the ejection curves produced by injecting fluid at various forces into the aorta and pulmonary artery of cadavers with the ballistocardiogram produced by this injection. Nickerson[5] constructed a heart-aorta model and studied the effects of variation of the length of the aorta on the K wave of the low-frequency ballistocardiogram. Another approach to the problem has been correlation of the temporal relationships of the ballistocardiographic waves with other measured physiologic events, namely, carotid-jugular pulse, heart sounds, and electrocardiograms. There have been numerous studies on the comparison of ballistocardiograms in diseased patients with those in healthy subjects. The evaluation of the effects of various drugs on the ballistocardiogram in patients, as well as in animals, has been in progress in recent years. Although these studies have yielded much information as to the mechanisms involved, the need for investigation of factors affecting the ballistocardiogram by more direct methods is obvious. The present report represents the effects on the dog ballistocardiogram of temporary occlusion of the venae cavae, aorta, and pulmonary artery.

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MATERIALS AND METHODS

The ballistocardiogram, carotid jugular pulse or aortic pressure pulse, and a limb-lead electrocardiogram were recorded simultaneously by means of a Sanborn Poly-Viso recorder. The bellows air-conduction system and piezoelectric transducer were utilized to obtain displacement ballistocardiograms directly from the head, as in humans, by the method described by Frederick and associates.[6] The carotid-jugular pulse was taken in three dogs by means of a glycerine capsule connected to a piezoelectric transducer. The aortic pressure pulse was recorded in the remaining dogs with a Sanborn electromanometer connected by means of an 18-gauge needle to a 9-inch length of polyethylene tube inserted through the right carotid artery into the aorta. The lag of this electromanometer was tested in comparison with that of the piezoelectric transducer and found to be less than 5 milliseconds.

The dogs were anesthetized prior to the operative procedures in the manner described by Frederick and associates.[6] The chest was opened by means of a full-length, midsternal incision, and the azygos vein was ligated in all dogs prior to experimental procedures. Size 2 black braided-silk suture material was used to occlude the vessels. The temporary occlusion of the venae cavae immediately outside the pericardial sac was accomplished by passing a loop of the suture material around the vessels and through a short segment of rubber tubing. Lifting this string and then clamping it in such a manner as to press one end of the rubber tubing firmly against the vessel wall served to effect complete occlusion. Release of the clamp on this string permitted patency of the vessel to be re-established quickly. The aorta and pulmonary artery were occluded similarly with one string passed through the transverse sinus at the base of these vessels within the pericardial sac. The duration of occlusion of the vessels was sufficiently long to obtain tracings of several heart cycles after equilibrium was established. Records were taken immediately before, during occlusion, and after recovery, following re-establishment of patency of the vessels. Fifteen observations were made in nine dogs before, during, and after occlusion of the superior and inferior venae cavae. Nine similar observations were made while the aorta and pulmonary artery were occluded, with the heart rendered nearly empty of blood by occluding the venae cavae a few beats earlier; and seven were made with all vessels occluded when occlusion of the outflow preceded the inflow by a few heart beats.

Occlusion of the inferior venae cavae by injecting 5 ml. of normal saline into a balloon catheter was performed on two occasions in one dog with closed chest. This balloon catheter was introduced through the right external jugular vein, and the position of the catheter just inferior to the right auricle was confirmed by opening the chest after conclusion of the experiment. Normal saline (30 ml.) was injected directly into the pericardial sac, producing acute cardiac tamponade in one dog with open chest.

Five of the dogs were cooled to a rectal temperature of 30° to 31° C. by placing them in a bin of chipped ice prior to operation. This resulted in persistence of a relatively slow heart rate throughout the experimental procedures.

TABLE I. EFFECTS OF OCCLUDING THE INFLOW AND OUTFLOW OF BLOOD TO AND FROM THE HEART ON THE DOG BCG

	VENOUS INFLOW OCCLUDED			INFLOW AND OUTFLOW OCCLUDED					
				INFLOW OCCLUDED FIRST			OUTFLOW OCCLUDED FIRST		
	NO. OF OBSERVATIONS	MEAN OF CONTROLS	MEAN OF OCCLUSIONS	NO. OF OBSERVATIONS	MEAN OF CONTROLS	MEAN OF OCCLUSIONS	NO. OF OBSERVATIONS	MEAN OF CONTROLS	MEAN OF OCCLUSIONS
Cycle (sec.)	15	0.580	0.540	9	0.691	0.534	7	0.634	0.600
Q to G (sec.)	13	0.039	0.038	7	0.037	0.033	6	0.042	0.037
Q to H (sec.)	13	0.068	0.063	7	0.073	0.061	7	0.069	0.066
Q to I (sec.)	15	0.105	0.097	9	0.114	0.097	7	0.100	0.090
Q to J (sec.)	15	0.159	0.147	9	0.172	0.139	6	0.160	0.140
Q to K (sec.)	14	0.216	0.198	9	0.231	0.189	7	0.214	0.211
Amplitude G-H (mm)	15	4.30	4.23	9	4.83	4.17	7	3.64	4.07
Amplitude H-I (mm)	15	8.70	8.60	9	9.10	9.44	7	9.64	9.14
Amplitude I-J (mm)	15	12.73	8.07	9	14.44	9.28	7	13.00	12.14
Amplitude J-K (mm)	15	10.60	4.63	9	13.11	6.78	7	11.00	9.57

The variations in the numbers of observations are due to lack of certainty about the identification of waves in a few records. The controls in this table refer to records taken immediately prior to the occlusion experiments.

All records were taken with the dog in the expiratory phase following the cessation of artificial respiration as described by Frederick and associates.[6] It was possible to obtain records of several heart cycles during these experiments before the dogs attempted spontaneous respiration.

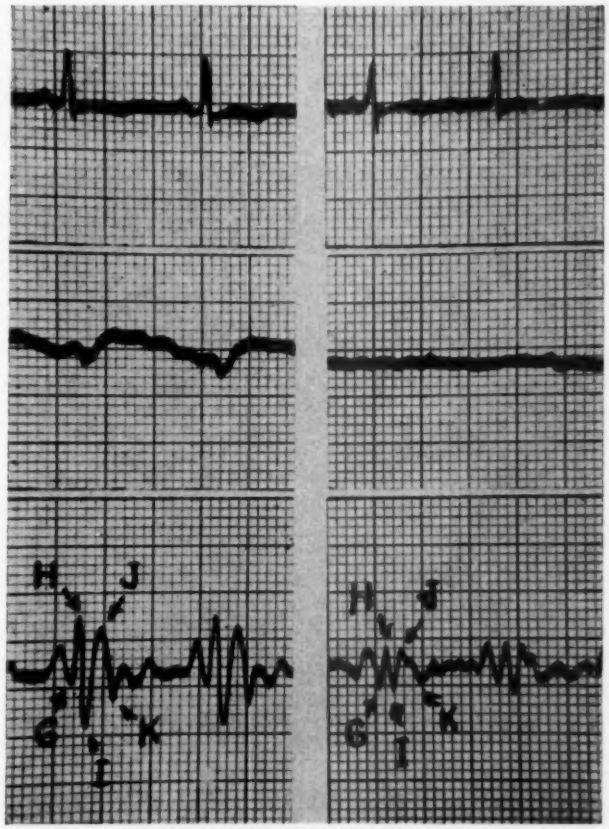

Fig. 1.—Simultaneously recorded limb Lead II electrocardiogram (upper tracings), carotid jugular pulse (middle tracings), and ballistocardiogram (lower tracings) in a dog immediately prior to (left) and during occlusion of the venae cavae (right). Note the preservation of the G-H-I-J-K waves without significant alteration in time relationships, though diminution of amplitudes occurs upon occlusion of the venous return to the heart.

RESULTS

Effects of Occlusion of the Venae Cavae.—The mean time interval from the onset of the QRS to each of the systolic waves of the ballistocardiogram is given in Table I. The control column in this table refers to records taken immediately prior to the occlusion experiments. It may be seen from this table that there is a slight shortening of all the mean time values for all waves during the occlusion of the venae cavae, but the degree of this change is within the error of measurement. The mean amplitudes of the systolic waves in the ballistocardiogram in both the control and experimental occlusions of the venae cavae are also given in Table I. There were no significant changes in the mean amplitudes of the G-H upstroke and H-I downstroke upon occlusion of the venae cavae. The

mean amplitudes of the I-J upstroke and J-K downstroke were considerably reduced upon occlusion of the venae cavae. The amplitudes of these waves returned toward the preocclusion control values when patency of the veins was re-established. Fig. 1 is a representative example of the experiments in which a reduction of the I-J upstroke and J-K downstroke occurred. These changes occurred in all but two of the animals; and in these two dogs, there were increases in the amplitudes of all systolic waves when the venae cavae were occluded. Fig. 2 is an example of an increase in the I-J upstroke and J-K downstroke which occurred in two animals.

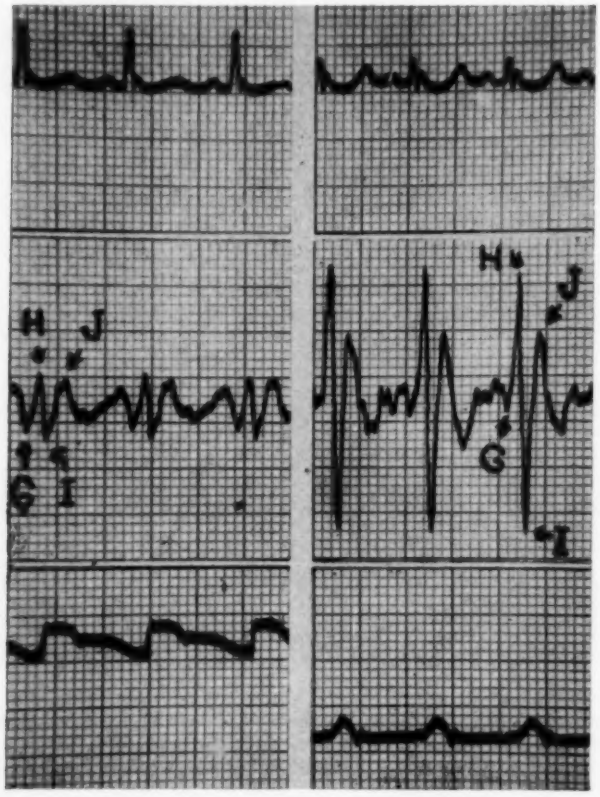

Fig. 2.—Simultaneously recorded limb Lead II electrocardiogram (upper tracings), ballistocardiogram (middle tracings), and aortic pressure pulse (lower tracings) in a dog immediately before (left) and during occlusion of the venae cavae (right). Note the increase in amplitudes of the G-H-I-J-K waves without significant alteration in the time relationships. There is a decrease in blood pressure from 100/85 mm. Hg in the control to 45/35 mm. Hg during occlusion of the venae cavae. The period of ejection systole is reduced by about 0.18 sec. following occlusion of the venae cavae, due to the shortening of the Q to aortic incisura time from 0.38 sec. to 0.18 sec., while the Q to the beginning of the aortic upstroke time is decreased by only 0.02 sec.

Occlusion of the Aorta and Pulmonary Artery Following Occlusion of the Venae Cavae.—The mean time intervals following the onset of the QRS and the mean amplitudes of the systolic waves of the ballistocardiogram are given in Table I. The mean time interval following the onset of the QRS for each of the systolic waves agreed fairly closely with the preocclusion controls. There

were no significant changes in the amplitudes of the G-H upstroke and the H-I downstroke. Diminution in the amplitudes of the I-J upstroke and the J-K downstroke in this circumstance occurred, as is illustrated in Fig. 3. However, increases in these amplitudes resulted in two dogs, as illustrated in Fig. 4. The reductions in the amplitudes of the I-J upstroke and the J-K downstroke in general were less marked than in those cases of occlusion of the venae cavae alone.

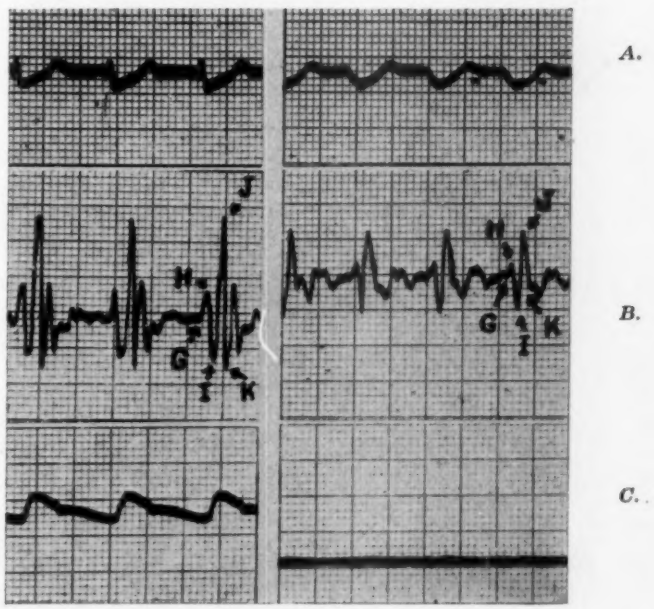

Fig. 3.—Simultaneously recorded limb Lead II electrocardiogram (upper tracings), ballistocardiogram (middle tracings), and aortic pressure pulse (lower tracings) in a dog immediately prior to (left) and during occlusion of the venae cavae, aorta and pulmonary artery (right). The venae cavae were occluded a few heart cycles before the arteries were occluded. There is preservation of the G-H-I-J-K waves of the ballistocardiogram in their normal time relationships, though a reduction in amplitude of the waves occurs upon occlusion of the great vessels in the above sequence. Note the absence of ejection of blood during the occlusion experiment.

Occlusion of the Aorta and Pulmonary Artery Prior to Occlusion of the Venae Cavae.—The values for the time intervals and amplitudes of the systolic waves of the ballistocardiogram are given in Table I. Fig. 5 is representative of the changes which occurred in these experiments. This sequence of occlusion was not performed in the two animals which showed an increase in the amplitudes of all waves upon occlusion of the venous inflow prior to occlusion of the outflow. The temporal relationships of the various systolic waves agreed fairly closely with the preocclusion controls. There were also no significant changes in amplitudes of the G-H upstroke and the H-I downstroke in this series. The I-J upstroke and J-K downstroke increased in amplitude in two animals, while

these amplitudes decreased in the remainder of the animals. However, the diminutions in these amplitudes were not as marked as those where the inflow had been occluded prior to occlusion of the outflow.

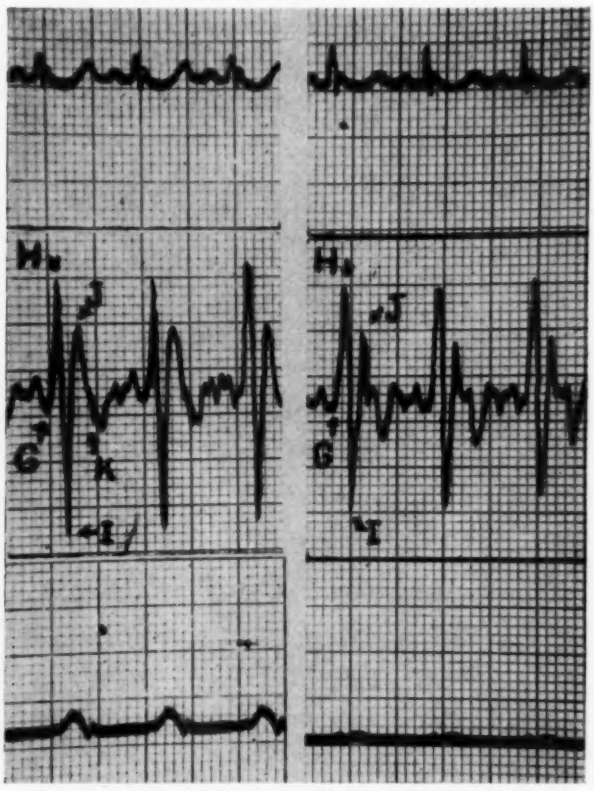

Fig. 4.—Simultaneously recorded limb Lead II electrocardiogram (upper tracings), ballistocardiogram (middle tracings), and aortic pressure pulse (lower tracings) in a dog with occluded venae cavae (left) and with the aorta and pulmonary artery subsequently occluded (right). Note the similarity of the ballistocardiograms in amplitude time relationships of the wave. There is obliteration of the aortic pressure pulse on the right, while a small pulse pressure is present on the left.

Other Observations.—The occlusion of the inferior vena cava on two occasions in one animal with closed chest produced reduction in the amplitudes of the I-J and J-K strokes similar in degree to that occurring after occlusion of the venae cavae in the animals with open chests. The time intervals of the systolic waves again agreed closely with the preocclusion and post-occlusion controls. The injection of 30 ml. of normal saline into the pericardial sac of one dog also produced marked reduction in the amplitudes of the I-J and J-K movements without significant alteration of the time relationships.

Multifocal premature ventricular contractions occurred in some animals after repeated experimental manipulations of the heart and vessels, and in one animal in the initial control record. The pattern of the ballistocardiogram varied strikingly with different foci of ventricular premature contractions, even

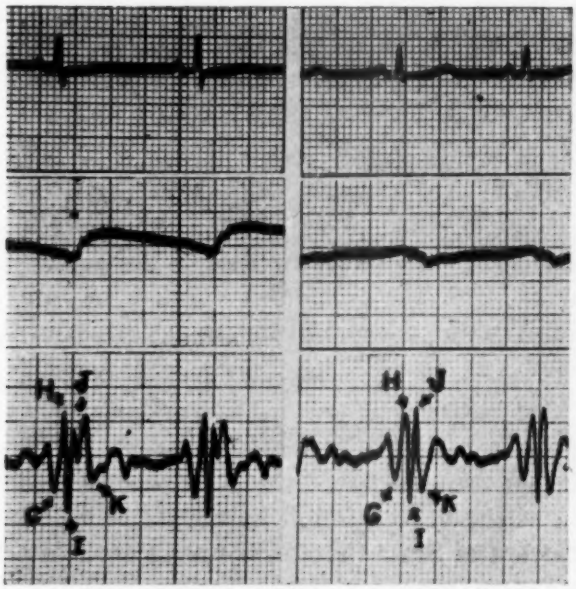

Fig. 5.—Simultaneously recorded limb Lead II electrocardiogram (upper tracings), carotid-jugular pulse (middle tracings), and ballistocardiogram (lower tracings) immediately before (left) and during occlusion of the venae cavae, aorta, and pulmonary artery (right). Occlusion of the arteries preceded occlusion of the venae cavae by a few heart beats. There is only slight reduction in the amplitudes of the waves of the ballistocardiogram upon occlusion of the great vessels in this sequence.

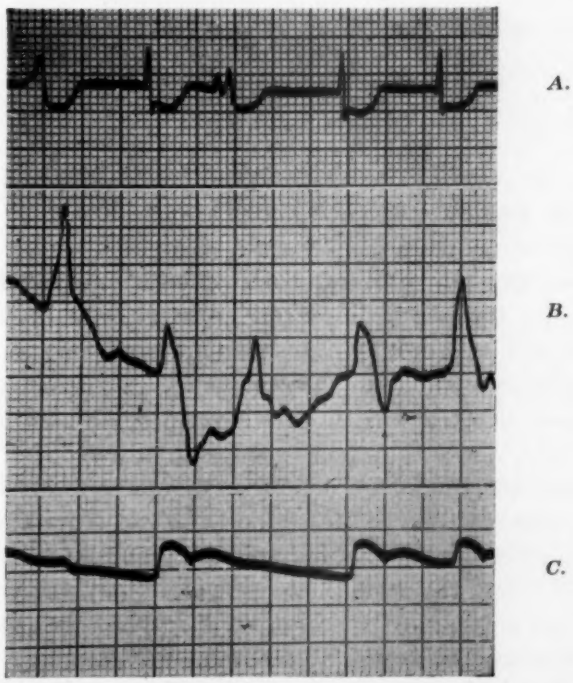

Fig. 6.—Simultaneously recorded limb Lead II electrocardiogram (*A*), ballistocardiogram (*B*), and aortic pressure pulse (*C*) in dog with closed chest. There is an idioventricular rhythm and an abnormal ballistocardiographic pattern. Note that the two extrasystoles from a different foci are followed by abnormal ballistocardiographic complexes though only a very small pulse is produced in the first instance and none in the second.

when the aortic pressure pulse contours were grossly similar and of equal amplitude. Fig. 6 is a portion of a record taken in a dog with an abnormal rhythm in which a bizarre ballistocardiographic complex of good amplitude occurred following each ECG complex, even when there was no rise in the aortic pressure.

Examination of the ventricular cavities immediately after death of one dog following occlusion of the great vessels, when occlusion of the veins preceded the arteries by several heart cycles, revealed about 20 ml. of blood in the right ventricle and about 25 ml. in the left ventricle. This probably represents residual blood plus drainage from the pulmonary vascular bed and cardiac musculature during the several minutes lapsing between occlusion of the great vessels and death of the animal.

DISCUSSION

The reduction in the amplitudes of the I-J upstroke and the J-K downstroke upon occlusion of the venous inflow to the heart is in keeping with the generally accepted concept of Starr that these waves are related to the impact of blood in the pulmonary artery and aortic arch. However, the presence of these systolic waves of the ballistocardiogram, even when there is no flow of blood in either the aorta or pulmonary artery and no ejection of blood from the ventricles, suggests that other factors play a part in the genesis of these waves. Furthermore, the increase in amplitudes of all systolic waves upon occlusion of the venae cavae, as was observed in two animals, is not readily explainable on the basis of impact of blood.

A quick footward jerk was easily palpable at the bases of the aorta and pulmonary artery during systole in our experimental animals. It seems probable that this traction on the great vessels is a significant factor in the genesis of the ballistocardiogram. The fact that multifocal premature contractions produced different BCG patterns without gross change in the amplitude or contour of the aortic pressure pulse would seem to indicate that the sequence of fractional contractions of the ventricular muscles may be one of the significant determinants of the ballistocardiographic pattern. It is possible that intracardiac blood flow and impact may have been factors in the genesis of the ballistocardiogram in these experiments. The presence of a small amount of blood in the ventricles upon death of the animal several minutes following occlusion of the great vessels is evidence that these studies do not separate entirely the forces of cardiac muscular contraction from those of intracardiac blood flow and impact. However, the quantity of the blood ejected from the left ventricle following occlusion of the venae cavae is extremely small, as can be seen by reference to Figs. 1 and 2; and the onset of ejection is slightly delayed in most instances and the incisura occurs markedly earlier than in the controls. Such an abridgment of systole has been observed by Opdyke and Wiggers,[7] who recorded right ventricular pressure during severe oligemia. Changes in the time relationships of ejection systole without comparable changes in the time relationships of the waves of the ballistocardiogram seem to indicate that other factors than impact of blood are significant in the genesis of these waves.

The reduction in amplitudes of the I-J upstroke and the J-K downstroke which occurs following occlusion of the venae cavae may be in part a manifestation of Starling's law of initial length of individual fibers, and, in part, a reduction of blood flow in the aorta, pulmonary artery, and ventricles. Occlusion of the aorta and pulmonary artery eliminates flow of blood in these vessels but does not eliminate intracardiac flow and impact of blood. The differences in amplitudes, observed when occlusion of the outflow preceded that of the inflow, may also be in part a manifestation of Starling's law as well as the intracardiac blood flow and impact. However, the fact that an increase in the amplitudes of the waves of the ballistocardiogram can occur upon occlusion of the venae cavae, aorta and pulmonary artery indicate that other factors must come into play. The influence of reflex sympathetic nerve impulses upon the heart resulting from drastic changes in blood pressure cannot be evaluated in these experiments, since the heart was not isolated from its nerves. It is conceivable that sympathetic stimulation of the heart causing more vigorous muscular contraction may result in an increase in the amplitude of the ballistocardiogram even in a nearly empty heart where the initial length of the fibers is less and when the ejection of blood is reduced or absent.

SUMMARY

1. No significant changes in the temporal relationships of the systolic ballistocardiographic waves were observed upon occlusion of the venae cavae in fifteen experiments on nine dogs. The amplitudes of the G-H upstroke and the H-I downstrokes were unchanged also, while the I-J upstroke and the J-K downstroke were diminished in amplitude. There was an increase in the amplitudes of all systolic waves in two dogs upon occlusion of the venae cavae.

2. Occlusion of the arterial outflow preceded by occlusion of the venae cavae also resulted in a persistence of the ballistocardiographic pattern in nine observations. Diminution in amplitudes of the I-J upstroke and the J-K downstroke was less marked here than with the occlusion of the venae cavae alone.

3. Occlusion of the aorta and pulmonary artery followed by occlusion of the venae cavae resulted in an increase in the I-J and the J-K amplitudes in two dogs while five dogs showed decrease in these amplitudes, but to a less extent than when the venae cavae were occluded first.

4. These observations indicate that the process of ventricular contraction may be an important determinant of the G-H-I-J-K sequence of the ballistocardiogram, apart from the forces of impact and flow of blood in the aorta and pulmonary artery.

SUMMARIO IN INTERLINGUA

Es presentate un studio del effectos notate in le ballistocardiogramma del can post que le fluxo sanguinee in e ab le corde esseva temporarimente interrumpite. Sub iste conditiones le configuration ballistocardiographic persiste

sin alterationes significative in le relationes temporal del undas. Le amplitudes median del movimentos I-J e J-K es reducite quando le influxo venose verso le corde es interrumpite. Le occlusion del effluxo arterial immediatemente ante le occlusion del venas cave resulta in allargate amplitudes del movimentos I-J e J-K. Sub iste conditiones le amplitudes del movimentos G-H e H-I remane sin alteration.

Le supra-describite observationes indica que—ultra le fortias del impacto e del fluxo de sanguine in le arteria pulmonar e in le aorta—le fortias de contraction muscular del corde es possibilemente un factor importante in le determination del ballistocardiogramma.

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CERTAIN CARDIOVASCULORENAL EFFECTS OF HEXAMETHONIUM

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HEXAMETHONIUM compounds recently have been used extensively in England, especially in the so-called bloodless surgery, and in various medical centers there and elsewhere in the treatment of hypertension. The hypotension produced by these drugs does not seem to be of brief duration. Hexamethonium acts by blockade of autonomic ganglia—both sympathetic and parasympathetic. With associates,[1] I was able to produce disturbances in renal function, and lesions of the kidney of various degrees, consequent to reduction of blood pressure by experimental hemorrhage, induced under aseptic precautions. It then became of interest to assess the effects of hexamethonium on the cardiovasculorenal system with special emphasis on renal hemodynamics and production of urine.

Ford and associates[2] reported that hexamethonium, when used orally in treatment of hypertension, caused no significant alterations in clinical status which might originate in impaired excretion of nitrogenous substances or in retention of sodium and water. Murphy and Eastwood[3] noted that on the use of one subcutaneous injection a day of 20 per cent hexamethonium bromide in polyvinylpyrrolidone, the minimal blood pressure was reached within the first 4 hours and appreciable hypotensive effects were apparent for as long as 12 hours. Rakita and Sancetta[4] concluded that hexamethonium lowers the arterial pressure of man primarily by diminishing total peripheral resistance rather than by diminishing cardiac output, while Murphy and associates[5] concluded from studies on anesthetized animals that the fall in blood pressure following intravenous administration of hexamethonium bromide is associated with significant decrease in cardiac output rather than with reduced peripheral resistance. McQueen[6] (with Trewin) found "evidence that abolition of tone in glomerular vessels tends to compensate for fall in blood pressure." They continued, "In patients with poor renal function, a severe fall in blood pressure produces severe and prolonged functional impairment. The fall in urine flow is of greater magnitude and longer duration than the fall in glomerular filtration

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rate." In an assessment of complications of controlled hypotension in anesthesia, Hampton and Little[7] concluded that "controlled hypotension" is truly "physiologic trespass." They reported that anuria was encountered in 54 of 549 cases in which complications occurred, and that renal failure was the cause of 8 of 46 reported deaths in the 21,000 cases of the survey. To decrease the number of complications they suggested that the systolic blood pressure be maintained at, or above, 80 mm. Hg.

Reynolds and others[8] obtained, in 15 of 17 cases, a reduction in splanchnic blood flow proportionate to the fall in arterial blood pressure, by intramuscular injection of hexamethonium bromide, 1 mg. per kilogram of body weight. They noted no change in splanchnic vascular resistance and stated that this indicated the absence of splanchnic vasodilatation. Mackinnon,[9] using pentamethonium iodide, obtained a reduction in renal blood flow and glomerular filtration rate and a rise in renal resistance. Gilmore and associates[10] suggested arteriolar dilatation as the explanation for the fall in blood pressure when the cardiac output was not significantly changed after administration of hexamethonium bromide. Miles was one of a group of co-authors[11] who reported that the renal circulation was largely uninfluenced by the fall in blood pressure brought about by pentamethonium bromide.

METHODS

This study was made on dogs anesthetized by intravenously administered pentobarbital sodium (approximately 25 mg. per kg.). Systolic and diastolic blood pressures in the systemic and pulmonic circuits were recorded on photosensitive paper by use of strain gauges connected to cardiac catheters. After heparinization of the animal a double-lumen catheter was introduced through the jugular vein, right atrium, and right ventricle until its tip passed some distance into the main trunk of the pulmonary artery. The lateral orifice was determined to be in the right ventricle. In some experiments in which the wedge pressure was recorded, the catheter was pushed farther into the pulmonary vessels until its tip was wedged in one of the smaller branches, while the lateral orifice remained in a main trunk of the pulmonary artery. Another double-lumen catheter was passed through either the femoral or carotid artery until its tip was determined to be in the cavity of the left ventricle and the lateral orifice was in the aorta, some distance above the aortic valves. The cardiac output was recorded by the Fick principle, in which oxygen consumption is determined, and samples of blood were taken from the left ventricle (arterial) and from the pulmonary artery (venous). The heart rate was determined from the electrocardiogram and the cardiotachometer tracing.

Renal blood flow was measured directly, by use of a bubble flowmeter connected between the renal and femoral veins. The manner of this connection was as follows: the affluent limb of the flowmeter was connected with the renal vein at the hilus of the kidney and the effluent limb with the central end of the distally ligated femoral vein. The flow of urine through cannulas inserted in the ureters above their entry into the bladder was recorded in milli-

liters per 5 minutes. To insure good flow of urine, about 50 c.c. of water per kilogram of body weight had been given by mouth before the anesthetic was administered and 5 per cent of glucose in saline solution, by intravenous drip, during the experiment.

After sufficient controls had been established on the pulmonic and systemic blood pressures, heart rate, cardiac output, renal blood flow and urine flow, one single intravenous injection of hexamethonium chloride, varying between 0.5 and 2 mg. per kilogram of body weight was given, and records were continued for at least 1 hour thereafter.

In several experiments the vagus nerves were isolated in the neck and were placed, intact, in shielded electrodes connected with an electric stimulator. Records were made of the effects of vagal stimulation on the blood pressures, heart rate, respiration, renal blood flow and urine flow before, and at various intervals after, intravenous injection of hexamethonium chloride.

TABLE I. MEAN CARDIOVASCULORENAL EFFECTS OF HEXAMETHONIUM CHLORIDE (MG./KG. I.V.) IN THE ANESTHETIZED ANIMAL

DETERMINATION MADE	CONTROL	AFTER HEX. CL.	MEAN DIFFERENCE	PER CENT CHANGE FROM CONTROL
Aortic pressure, mm. Hg				
Systolic	149 ± 14.9	94 ± 14.9	−55	−37
Diastolic	103 ± 19.8	68 ± 16.7	−35	−34
Lt. ventricle pressure, mm. Hg				
Systolic	156 ± 16.4	95 ± 15.5	−61	−39
Diastolic	12 ± 11.6	2 ± 5.9	−10	−83
Pulmon. art. pressure, mm. Hg				
Systolic	19 ± 2.7	13 ± 1.8	−6	−32
Diastolic	6 ± 3.1	3 ± 2.6	−3	−50
Rt. ventricle pressure, mm. Hg				
Systolic	24.4 ± 1.69	17.8 ± 1.85	−6.6	−27
Diastolic	1.40 ± 2.77	0.20 ± 1.655	−1.2	−86
Wedge pressure, mm. Hg				
Systolic	12 ± 0.5	6 ± 2.1	−6	−50
Diastolic	5 ± 2.3	2 ± 1.7	−3	−60
Cardiac output, L./min.	2.80 ± 0.419	1.95 ± 0.296	−0.85	−30
Cardiac rate, beats/min.	161 ± 14.84	131 ± 16.72	−30	−19
Renal blood flow, ml./min.	161.6 ± 8.4	71.8 ± 12.5	−89.8	−56
Urine flow, ml./min.	0.46 ± 0.06	0.18 ± 0.06	−0.28	−61
Total renal resistance, dynes sec. cm.$^{-5}$	53,067 ± 7,261.6	60,547 ± 14,130.6	+7,480	+14

RESULTS

The mean cardiovasculorenal effects of intravenously administered hexamethonium chloride on the anesthetized dog are presented in Table I. The

dose was 1 mg. per kilogram of body weight. Blood pressures, systolic and diastolic, in the aorta, left ventricle, pulmonary artery, and right ventricle were appreciably reduced (Table I). Wedge pressures also were reduced, the systolic pressure by one-half and the diastolic by approximately two-thirds. Cardiac output and cardiac rate, likewise, were reduced, the former by a little less than one-third and the latter by a little less than one-fifth. Reduction in renal blood flow and in the flow of urine approached two-thirds. The only instance of increase was in total renal resistance; this amounted to about one-seventh.

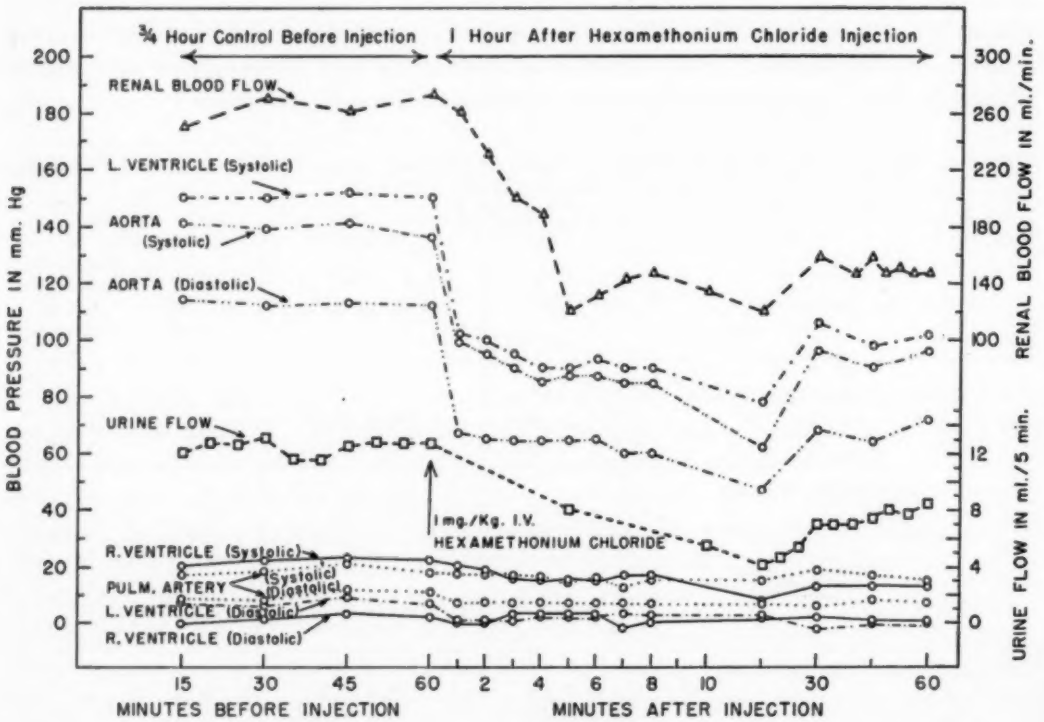

Fig. 1.—Simultaneous reduction in blood flow, blood pressure, and urine production effected by intravenously injected hexamethonium chloride.

In Fig. 1 it appears that the hypotensive effect of hexamethonium goes hand in hand with the renal ischemic effect and the depression of urine production by the kidney. Even the occurrence of the average maximal hypotension coincides with the average maximal reduction in renal blood flow and in production of urine. These findings give unequivocal support to the conception of the importance of blood pressure and blood flow in the manufacture of urine by the kidney. Fig. 2 demonstrates the persistent reduction in ventricular stroke volume and the fall in arterial blood pressure, in both systemic and pulmonic circuits, following administration of hexamethonium. In the original tracings, taken during various periods throughout the experiments, such effects lasted for several hours.

The influence of hexamethonium on vagal inhibition is clearly demonstrated in Fig. 3. Electric stimulation of the intact vagus nerves, before injection of hexamethonium, brought about the usual vagal inhibitory effects: namely, cardiac standstill, precipitous fall of arterial and ventricular blood pressure to zero, and cessation of respiration, followed by occasional escapes from vagal inhibition. Immediate return of original conditions occurred on termination

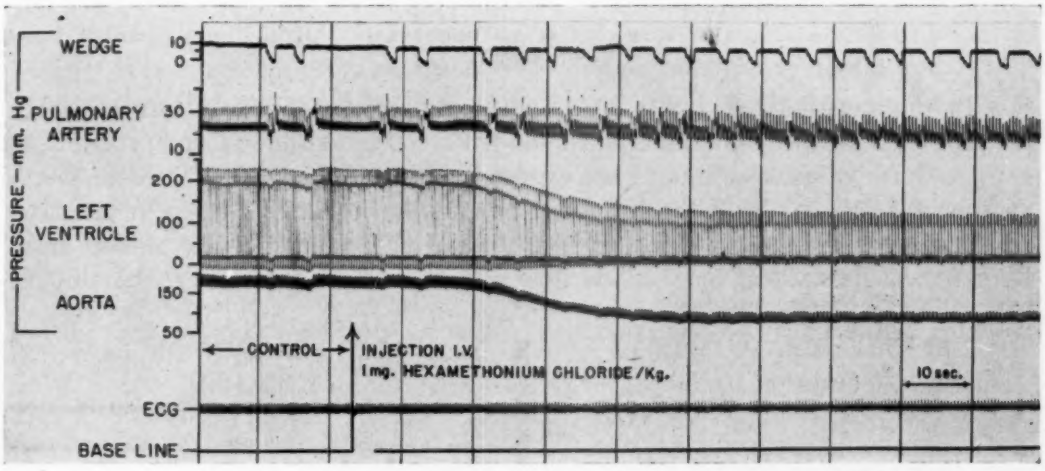

Fig. 2.—Reduction in ventricular stroke volume accompanying the reductions in blood pressure after administration of hexamethonium.

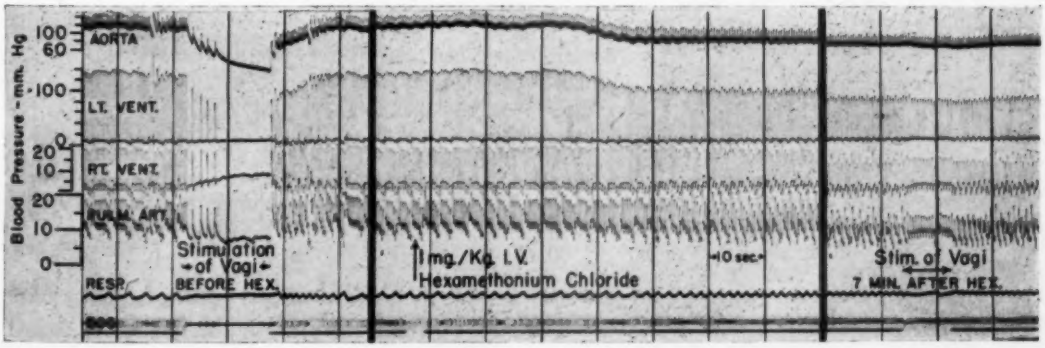

Fig. 3.—Disappearance, after administration of hexamethonium, of vagal inhibition and of its resultant cardiac standstill and marked fall in blood pressure during electric stimulation of the vagus nerves. Respiratory inhibition during vagal stimulation, however, was not abolished by hexamethonium.

of stimulation. However, after intravenous administration of hexamethonium chloride the vagal effects were quite different during electric stimulation of the intact vagus nerves. There were no cardiac standstill and no precipitous fall in arterial and ventricular pressures. Respiratory inhibition, however, did occur in the same manner as before administration of the drug. The heart rate was slightly slowed but the heart kept on beating during vagal stimulation at about the same magnitude as before injection of hexamethonium.

The action potentials recorded on a cathode-ray oscillograph from single afferent fibers carried with the vagus nerves from stretch receptors in the alveoli and the alveolar ducts of the lungs are shown in Fig. 4. The number of discharges from these fibers after intravenous injection of hexamethonium were the same as those recorded from the same fiber before injection of the drug. This can be considered good evidence that the effects of hexamethonium probably are limited to synapses in ganglia and that nerve fibers or nerve endings not relayed through autonomic ganglia probably are not affected.

SUMMARY

In the anesthetized dog, a study was made of the effects of intravenously administered hexamethonium chloride on the renal blood flow, urine production, cardiac output, heart rate, and the systemic and pulmonic blood pressures. A comparison was made of the influence of vagal stimulation on the heart rate, respiration, and blood pressure before and after administration of the drug. Direct measurement of renal blood flow was made by a flowmeter, the affluent

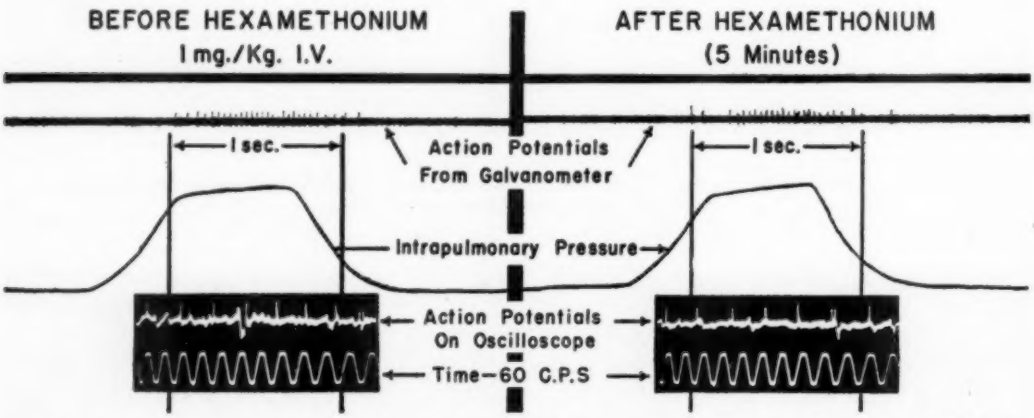

Fig. 4.—Demonstrating action potentials recorded from one afferent fiber carrying impulses from stretch receptors in the lungs. Note the absence of change in number or contour of action potentials recorded before and after administration of hexamethonium.

limb of which was connected to the renal vein at the hilus of the kidney and the effluent to the central end of the distally ligated femoral vein. This caused renal venous blood to pass through the flowmeter and ultimately to the vena cava via the femoral vein. Cardiac output was determined by the Fick principle. Systolic and diastolic pressures from the systemic and pulmonic systems were recorded on photosensitive paper by use of strain gauges connected to cardiac catheters.

Intravenously injected hexamethonium chloride caused considerable reduction in cardiac output and prolonged reduction in blood pressure and renal blood flow. These circulatory changes were accompanied by marked reduction in formation of urine. Hexamethonium caused a slight increase in renal resistance. The cardiac standstill and the precipitous fall in blood pressure produced by stimulation of the vagus nerves were abolished after administration

of hexamethonium. The action potentials recorded from afferent impulses obtained from stretch receptors in the lungs were not affected by the administration of hexamethonium.

SUMMARIO IN INTERLINGUA

In experimentos con canes le injection intravenose de chlorido de hexamethonium causava un considerabile reduction del rendimento cardiac e un prolongate reduction del pression sanguinee e del fluxo renal. Iste cambiamentos circulatori esseva accompaniate per un marcate reduction in le formation de urina. Hexamethonium causava un leve augmento del resistentia renal. Le arresto cardiac e le precipitose reduction del pression sanguinee, le quales resulta ordinarimente del stimulation del nervos vage, non se manifestava post le administration de hexamethonium. Esseva registrate le potentiales de action in afferente impulsos veniente ab receptores tensional in le pulmones. Iste potentiales non esseva afficite per le administration de hexamethonium.

The author wishes to express his gratitude for the excellent technical assistance rendered by Miss Irene Donovan and by Messrs. Robert Arns, Arthur Meeker, and Walter Ogg, as well as for the help of Dr. H. L. Davis in recording action potentials for Fig. 4.

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A COMPARISON STUDY OF DRUGS IN EXPERIMENTAL AND CLINICAL AURICULAR FIBRILLATION

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THE toxicity of quinidine limits its usefulness in the treatment of auricular fibrillation and indicates the need for better therapeutic agents for control of this arrhythmia. Search for such a drug, however, has been thwarted by lack of understanding of the underlying mechanisms causing auricular fibrillation and the difficulty in reproducing "clinical auricular fibrillation" in experimental animals. Despite the efforts of numerous investigators no satisfactory explanation of the pathophysiologic disturbances responsible for this arrhythmia has been forthcoming. Four theories of mechanism are currently discussed: (1) The classic circus movement theory (Lewis and associates[1]); its modified form, the re-entry theory (DeBoer[2], Mines[3]); the multiple ectopic focus theory (Englemann[4]); and, the single ectopic focus theory (Rothberger and Winterberg[5], Prinzmetal and associates[6]).

Quinidine's therapeutic action in auricular fibrillation has been attributed to its ability to prolong the myocardial refractory period. Recent studies have explored the use of agents prolonging the refractory period in the hopes that these drugs might prove effective in treating auricular fibrillation. Dawes[7] devised a simple, though indirect method, for the experimental measurement of the effect of drugs on the refractory period using the isolated rabbit auricle. By the use of this technique a number of antihistamines and closely related compounds were studied (McCawley and associates[8]). This study suggested that two drugs, the antihistamine, diphenhydramine hydrochloride (Benadryl), and the atropine-like drug, methantheline bromide (Banthine), were more effective than quinidine in prolonging the refractory period.

Since some question exists as to the relationship between drug-induced prolongation of the myocardial refractory period and an ability to convert auricular fibrillation to normal sinus rhythm,[9] it was evident that further experimental studies were required to determine whether or not Benadryl or Banthine was more effective than quinidine. The present report deals with further experimental studies using these new drugs to prevent, modify, or stop artificially produced auricular fibrillation in dogs. Following this, Benadryl and Banthine were subjected to clinical trial in patients with auricular fibrillation. In this type of study two objectives may be realized: (a) the development of a more useful therapeutic agent and (b) a closer understanding of the clinical arrhythmia.

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METHODS AND MATERIALS

1. *Experimental.*—Since there is no general acceptance of any of the four theories of the genesis of auricular fibrillation cited previously, no one of the experimental methods used to evoke artificially auricular fibrillation should be entirely depended upon. For this reason we made use of several selected experiments representative of each theory, following in all essential details the techniques described in the original reports.[5,10-12] In addition, the observation of Nahum and Hoff[13] that small doses of acetylcholine injected into hyperthyroid patients elicits transient auricular fibrillation was translated into animals. This was done by feeding normal dogs 2 Gm. doses of thyroid powder daily until frank signs of hyperthyroidism appeared. Periodically, the dogs were anesthetized with pentobarbital and graded doses of acetylcholine injected intravenously. Many of the animals then developed auricular fibrillation which persisted for 10 to 37 seconds. In these and the foregoing instances of experimentally produced auricular fibrillation Benadryl, Banthine, and quinidine were compared as to their ability to prevent or terminate the fibrillation.

2. *Clinical.*—Patients with auricular fibrillation, selected for therapeutic trial with Benadryl or Banthine, were those who would ordinarily be given quinidine therapy. Patients were hospitalized during the evaluation of all drugs. Most of the patients had extensive cardiac damage and several died subsequently as a result of the underlying cardiac disease. All patients with congestive heart failure were digitalized. No patient in uncontrolled thyrotoxicosis was included in the series. A period of several days was allowed to elapse before trial with the antifibrillatory drugs in order to rule out conversion of an arrhythmia by digitalis. All patients failing to respond satisfactorily to Benadryl or Banthine were later given quinidine. In all instances a Lead II electrocardiogram was recorded during the period of therapy.

RESULTS

Experimental Animal Auricular Fibrillation.—In each form of experimentally induced auricular fibrillation, approximate "minimal effective antifibrillatory" dosage was established. Benadryl and Banthine were compared with quinidine gluconate. Each drug was administered to a one dog at a dose of 1.0 mg. per kg.; the dosage was then doubled until an antifibrillatory effect was observed. The values cited in Table I are the smallest doses for converting or preventing fibrillation in two or more dogs. Doses one-half of those listed in Table I were either effective occasionally or not at all. In certain experiments it was possible to define the minimum effective threshold dose more accurately.

The results (Table I) indicate that Benadryl and Banthine are at least as effective as quinidine in altering experimental auricular fibrillation. There is, however, no evidence to indicate that Benadryl or Banthine are three to six times as potent as quinidine as had been suggested by previously reported studies on the prolongation of the myocardial refractory period. It may also be observed in Table I that auricular flutter requires higher doses of quinidine or Benadryl to effect conversion than does auricular fibrillation.

TABLE I. EVALUATION OF DRUGS IN EXPERIMENTALLY-INDUCED AURICULAR ARRHYTHMIAS

EXPERIMENTAL PROCEDURE	THEORY ON WHICH METHOD IS BASED	TYPE OF ARRHYTHMIA	DOSE OF DRUGS REQUIRED TO RE-ESTABLISH NORMAL RHYTHM OR PREVENT ARRHYTHMIA (MG./KG.)		
			QUINIDINE GLUCONATE	BENADRYL HYDRO-CHLORIDE	BANTHINE BROMIDE
Topical acetyl-choline	Multiple ectopic focus (Scherf et al.[11])	Fibrillation	2	1.5	2
Direct faradization of auricle "Nachflimmern"	Single ectopic focus (Rothberger and Winterberg[5])	Irregular	4	1–2	2
Subepicardial aconitine	Single ectopic focus (Scherf and Terra-nova[10])	Flutter	2	2	2–4
Crush infarct and faradization	Circus movement (Rosenblueth and Garcia Ramos[12])	Flutter	10–12	2	6
Crush infarct and faradization	Circus movement (Rosenblueth and Garcia Ramos[12])	Fibrillation	4	2	2
Acetylcholine-thyrotoxicosis	"E" factor (Nahum and Hoff[13])	Fibrillation	2.5	2.5	1.0

Clinical Auricular Fibrillation.—Auricular fibrillation was converted to normal sinus rhythm in eleven of seventeen patients given Benadryl.[14] In another group of seventeen patients, ten were converted by quinidine. None of the eleven patients who received Banthine showed any change in their arrhythmia (Table II). One patient required a combination of Benadryl and quinidine therapy, as neither drug alone had been effective. The six patients who failed to respond to Benadryl were later given the usual oral quinidine therapy; of these, four converted to normal sinus rhythm.

TABLE II. COMPARATIVE TRIAL THERAPY OF BENADRYL, BANTHINE, AND QUINIDINE IN CLINICAL AURICULAR FIBRILLATION

DRUG	RESTORATION OF NORMAL CARDIAC RHYTHM (NUMBER PATIENTS RESPONDING/TOTAL NUMBER PATIENTS)		
	RECENT AURICULAR FIBRILLATION DURATION LESS THAN 30 DAYS	CHRONIC AURICULAR FIBRILLATIONS DURATION 2 MONTHS TO 6 YEARS	TOTAL
Benadryl Hydrochloride	9/10	2/7	11/17
Banthine Bromide	0/3	0/8	0/11
Quinidine Hydrochloride	4/7	6/10	10/17

Several effects of Benadryl on the heart were revealed during its trial in auricular fibrillation. These actions may be compared to the actions of quinidine. The patients with auricular fibrillation were divided into two groups; those whose arrhythmia developed recently (less than 30 days) and those whose fibrillation was known to have been present for periods of two months to six years. When the results of each group were studied, Benadryl was found to restore to normal rhythm nearly all (9/10) of the "recent fibrillators" while few (2/7) of the "chronic" fibrillators responded.* The differences between recent and chronic fibrillating patients on quinidine therapy are less striking (Table II). Results similar to those seen with Benadryl[15] have been reported with Pronestyl (procaine amide), a drug which has been observed to cause therapeutic conversion only of recent auricular arrhythmias. This is not an unexpected finding as both Pronestyl and Benadryl are chemical derivatives of dialkylaminoethanol. Diethylaminoethanol itself is known to prevent or reverse various types of cardiac arrhythmias though excessive doses are required.

A precisely accurate comparison of antifibrillatory potency for Benadryl and quinidine was not made because of the inherent difficulties of clinical investigation. Six patients resumed a normal sinus rhythm after a single 100 mg. dose of Benadryl given intravenously. The others responded only to 200 to 300 mg. doses. It is possible that "successful therapeutic result might have been obtained in the six failures" had larger doses of Benadryl been given. The largest dose given to any patient at one time was 400 mg. Although no serious side effects appeared, other than the expected sedative-hypnotic action, the development of muscle twitching suggested possible toxic effects. One patient developed sufficient side actions to necessitate cessation of therapy after 180 mg. of Benadryl had been injected. In order to make a more direct comparison of the dosages of Benadryl and Banthine, with that of quinidine, four patients were given quinidine gluconate by the intravenous route. The doses used were: 200, 400, and 800 mg., using a very slow rate of administration to avoid hypotension and other toxic effects. One patient, given 400 mg. Banthine without success, converted to normal sinus rhythm after 400 mg. quinidine gluconate was administered intravenously. Similarly, another patient responded to this dose of intravenous quinidine, though 300 mg. of Benadryl intravenously had no effect. The remaining thirteen patients used for comparison in this study received quinidine hydrochloride by mouth in the usual manner. Five patients failed to tolerate a total daily dose of 3 Gm. because of tinnitus, vomiting, and diarrhea. Only one of these converted to normal sinus rhythm (1.0 Gm. daily dose). It is suggested that these patients might have been restored to normal sinus rhythm on a greater dose of quinidine had not "cinchonism" interfered.

The electrocardiographic changes occurring during Benadryl therapy in patients were similar to those seen with quinidine. Benadryl, like quinidine, caused an increase in ventricular rate, presumably by a vagolytic action. The

*It is generally assumed that recent auricular fibrillation is paroxysmal in nature, and spontaneous conversion may occur at any time. The fact that the patients receiving Benadryl changed to normal rhythm within 14 to 58 minutes after the intravenous administration of the drug would appear adequate to rule out a fortuitous result.

pulse rate during fibrillation speeded up 10 to 40 beats per minute, and this increase occurred whether or not the patients had been adequately digitalized. The ventricular rates, after Benadryl had caused conversion to normal sinus rhythm, were within normal values. A similar increase in the irregular ventricular rate of auricular fibrillation was the only electrocardiographic change observed following the administration of Banthine. Benadryl caused an unexpected decrease in the Q-T interval. The mean Q-T interval, before Benadryl had been given was 0.33 sec. (range 0.28 to 0.42 sec.) while the mean Q-T interval during the peak of the drug action was 0.31 sec. (range 0.24 to 0.38 sec.). At the dosage used there was no prolongation of the QRS interval. In animals we have observed that Benadryl can prolong both the QRS and Q-T intervals as can quinidine. There was, however, some clinical evidence for an effect of Benadryl on myocardial conduction. During the transition period of Benadryl's conversion of auricular fibrillation to normal sinus rhythm, several types of disturbance were seen. These consisted of bundle branch block, incomplete heart block with occasional premature systoles, and runs of A-V nodal rhythm. These temporary alterations in rhythm were also seen during quinidine therapy. A patient who had a long-term auricular fibrillation developed a myocardial infarction. During the convalescent period following this episode he developed a ventricular tachycardia. Benadryl (100 mg.) was given intravenously over a 20-minute period. Fifteen minutes after the start of the infusion the ventricular tachycardia changed to auricular fibrillation. Ten minutes later the patient converted to normal sinus rhythm. This case suggests that Benadryl, like Pronestyl,[15] is more effective in ventricular than in atrial arrhythmias.

DISCUSSION

Comparison of the animal-experiment data with the clinical results reveals no satisfactory correlation between the two methods of drug evaluation. In particular, Banthine was shown to have greater antifibrillatory potency than quinidine in some of the experimental procedures. Yet, in no instance did it alter the fibrillation of the patients. Larger doses of both Benadryl and Banthine were given to some patients than had been predicted necessary from the animal data. A dose of 400 mg. to the average patient (weighing 70 kg.) may be expressed as 5.7 mg. per kg. As shown in Table I, it was noted that adequate doses for reversal of the various types of experimentally-induced auricular fibrillation were from 1 to 4 mg. per kg.

Certain factors, previously considered important in the theories of the basic mechanisms of auricular fibrillation, are challenged by this study. No longer tenable is the contention that a drug which prolongs the relative refractory period will necessarily prove effective in clinical auricular fibrillation. Van Dongen[9] has cited additional evidence for this viewpoint. It is conceivable that quinidine's prolongation of the refractory period may even constitute an undesirable side effect, e.g., in provoking bundle branch block and leading to ventricular arrhythmias.

The vagus is alleged to play an important role in auricular fibrillation by many investigators. Yet, when Resnick[16] produced adequate vagal paralysis by giving patients intravenous Atropine, fibrillation usually persisted. Our

own experience with Banthine, a parasympatholytic drug, indicates that the vagus plays a minor role in clinical auricular fibrillation.

This study suggests that although previously described experimental techniques undoubtedly illustrate factors initiating auricular arrhythmias, these arrhythmias are generally maintained only as long as the initiating stimulus persists. Clinical auricular fibrillation (paroxysmal and persistent forms) is influenced by unknown factors tending to maintain the arrhythmia. Nahum and Hoff[13] describe an unknown "E" (or excitatory) factor present in thyrotoxicosis which interacts with the vagus or vagomimetic substances to cause auricular fibrillation. They formulated the hypothesis that the "E" factor is present in other conditions associated with fibrillation. The factor might explain the high incidence of fibrillation in patients with mitral valve disorders. De la Chapelle and associates[17] noted that there was no relation between the grade of mitral stenosis and auricular fibrillation but that mitral stenosis or insufficiency was "necessary for persistent auricular fibrillation (not the transitory form) in rheumatic heart disease." The failure of drugs found effective in animal studies to alter chronic auricular fibrillation in human patients can be explained by the assumption that in clinical fibrillation the maintenance factor is dominant and the initiation cause no longer necessary. Therefore, it will be necessary to find and reproduce experimentally this unknown factor that maintains auricular fibrillation. Better methods for evaluating antifibrillatory drugs in animals will probably emerge leading to an understanding of the mechanism of auricular fibrillation.

SUMMARY

Each of four basic theories for the genesis of auricular fibrillation and flutter is supported by experimental procedures using laboratory animals. These procedures were used to evaluate certain compounds felt to have antifibrillatory properties. Drugs with high experimental antifibrillatory potency did not necessarily exhibit therapeutic action when subjected to clinical test. No basic theory as yet has sufficient experimental proof to explain completely the mechanism of auricular fibrillation.

Hypervagotonia is undoubtedly an important factor in the initiation of auricular fibrillation but not in the maintenance of the arrhythmia. An unknown factor (or factors) appears to be responsible for the maintenance of auricular fibrillation.

Diphenhydramine hydrochloride (Benadryl) may be added to the list of successful therapeutic agents for clinical auricular fibrillation. Although our results do not indicate it for routine use in place of quinidine, its use may prove valuable in selected patients. Banthine, while possessing the ability to prolong the myocardial refractory period and to prevent or reverse auricular fibrillation in experimental animals, did not prove effective in the treatment of auricular fibrillation in humans.

SUMMARIO IN INTERLINGUA

Cata un del quatro theorias promulgate per altere autores pro explicar le genese de fibrillation auricular es supportate per experimentos con animales

laboratorial. Nos ha empleate le procedimentos de ille experimentos pro evalutar le virtutes antifibrillatori de certe compositos chimic.

Il resultava que fibrillation inducite per methodos experimental es prevenite o revertite per le duo drogas diphenhydramina (Benadryl) e methanthelina (Banthine). Le duo esseva subjicite a essayos clinic. Methanthelina se provava totalmente inefficace in uso clinic ben que illo habeva essite le plus active agente antifibrillatori in experimentos animal. Illo prolonga le periodo refractori myocardiac e ha nulle valor therapeutic in le tractamento de patientes con fibrillation auricular. Del altere latere, diphenhydramina pote esser addite al lista de efficace agentes therapeutic in le tractamento de fibrillation auricular. Illo es probabilemente de valor in seligite casos.

Nostre datos experimental pare indicar que hypervagotonia es un factor importante in le initiation experimental de fibrillation auricular sed non in le mantenentia de iste arrhythmia como disordine clinic. Isto es mantenite per un factor (o factores) incognoscite.

Nostre studios indica que nulle del currente theorias in re le genese de fibrillation auricular es completemente satisfactori. Un revision es necessari.

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Critique

THE PHYSIOLOGIC THIRD HEART SOUND: ITS MECHANISM AND RELATION TO PROTODIASTOLIC GALLOP

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THE physiologic third sound, heard by Thayer in 70 per cent of normal teen-age subjects, and in over one-third of normals of all ages, was scarcely mentioned during the period of auscultatory pioneering which lasted for the whole of the nineteenth century. Potain,[1] who emphasized the gallop sounds and the opening mitral snap, taught for over three decades that such sounds in diastole occurred only in hypertrophied or dilated hearts. But what is generally accepted today was fully set forth by Barié in 1893. He wrote " . . . if one studies, by graphic methods, the curves of the pulse, the heart, and the jugular vein, one realizes quite clearly that the abnormal motion which causes the gallop sound is only an exaggeration of that which occurs normally in everyone, but without causing a perceptible noise. But in fact, if one auscults a large number of healthy subjects, one hears a little rudimentary sound, which, exaggerated, will become a gallop."[2] Obrastzow,[3] of Kiev, first claimed that a protodiastolic third sound was frequently present in healthy subjects. The fact that many masters of auscultation were unaware of this phenomenon can be ascribed to the use of the Laennec or monaural stethoscope, which is a poor conductor of low-frequency waves. Obrastzow used direct auscultation, while Thayer[4-6] used the binaural stethoscope. He also put his subject in left lateral decubitus, which doubles the relative loudness of the third sound.

Thayer accepted the explanation for this sound which had been suggested in 1906 and published a year later by his colleague and pupil, Hirschfelder.[7] In that year the same theory was offered independently and with more conviction by Gibson[8] of Oxford. Both men had observed, in a few subjects, a sharp early rise in the jugular pulse, following the v wave and early diastolic collapse, and had found third sounds in the same subjects. Other people, with no third sound, showed no such wave. Both investigators were familiar with Y. Henderson's account[9] of his study of valve function in a model heart used Edison's kinetoscope to take twelve pictures in 0.6 sec. This showed that the valves closed at the end of a phase of rapid inflow, ". . . especially noteworthy being the closing of the mitral in mid-diastole." While Thayer discussed two

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other possible mechanisms, he accepted Hirschfelder's and Gibson's thesis, that, after rapid inflow, reflux toward the auricles and great veins closed the leaflets, causing the sound and the rapid refilling of the jugular veins. This thesis was also accepted by Benjamin,[10] whose esophageal pulse waves from the left auricle showed a rise after the v wave, with a peak (IV, in Fig. 5 of his paper), 0.13 sec. after the second sound and synchronous with the third. The same view was accepted by Lewis and Dock,[11] who confirmed with modern techniques Barié's belief[2] that the apex thrust in early diastole ceased abruptly at the moment the third sound occurred. They also confirmed Wolferth and Margolies' evidence that protodiastolic gallops and third sounds showed similar relations to the apex thrust and the second sound.[12] Later, Brady and Taubman showed that with protodiastolic gallop or third heart sound there is a sharp inflexion of the outward motion of the left ventricular border, as recorded by slit- or electrokymography.[13]

Einthoven reported the third sound in a phonocardiogram[14] after Gibson had suggested to him that such a sound be sought in tracings from normals, in order to establish its time relations. Impressed by the fact that the sound was almost synchronous with the carotid incisura, he concluded that it arose in the root of the aorta. As this relation was not regularly observed, the theory found no favor with later students of the phenomenon.

Ohm[15] accepted Potain's theory that the third sound and protodiastolic gallop were due to vibrations set up in ventricular walls, stretched to capacity by a sudden inrush of blood, and this theory has satisfied most later authors, as noted by Leonhardt[16] and Mannheimer[17] in their reviews of the subject. Boyer and associates[18] concluded that the sound arose from the impact of the ventricle on the chest wall, although Thayer[5] had heard it in the exposed heart of the dog. Recently Eddleman and associates[19] concluded that the third sound arose in the A-V valves at the onset, not at the end, of ventricular expansion. They considered this a normal opening snap, and the editor commented, ". . . an exaggerated opening snap consequently is not necessarily indicative of mitral stenosis".[20]

Luisada[21] had reported an opening snap in normals, 0.04 sec. after the second sound, and 0.08 to 0.12 sec. before their third sound. All previous students had reported that snaps occurred 0.04 to 0.12 sec. after the second sound, in patients with mitral stenosis but never in normals, while third sounds and protodiastolic gallops in adolescents or adults occurred in the range 0.12 to 0.20 sec. Those who studied the venous pulse in patients with snap, found this sound occurring very close to the jugular v peak, while gallop and third sounds occurred farther down on the descending limb, or with the upturn after the early diastolic collapse. The claim that these accepted time relations of the third sound were in error, and the existing controversy over the origin of the third heart sound, led us to re-examine the older data and collect new evidence.

METHODS

After examining a large group of male high school students for third sounds, six were selected for study. Their third sounds covered the range from loud to very faint; all were seventeen years old and in excellent health.

At the initial examination all had Lead II of the electrocardiogram, the apical sounds and the apical impulses recorded while supine, in left lateral decubitus and sitting. A Cambridge string galvanometer and accessory equipment were used. Slit kymograms were made in the supine position, using a device which records 6 seconds of head-foot ballistocardiogram, and of Lead II of the electrocardiogram, with signals on the latter curve showing the instants of starting and stopping the 1.3 sec. roentgen exposure.[22] The slits are 15 mm. apart, and 1 mm. wide.

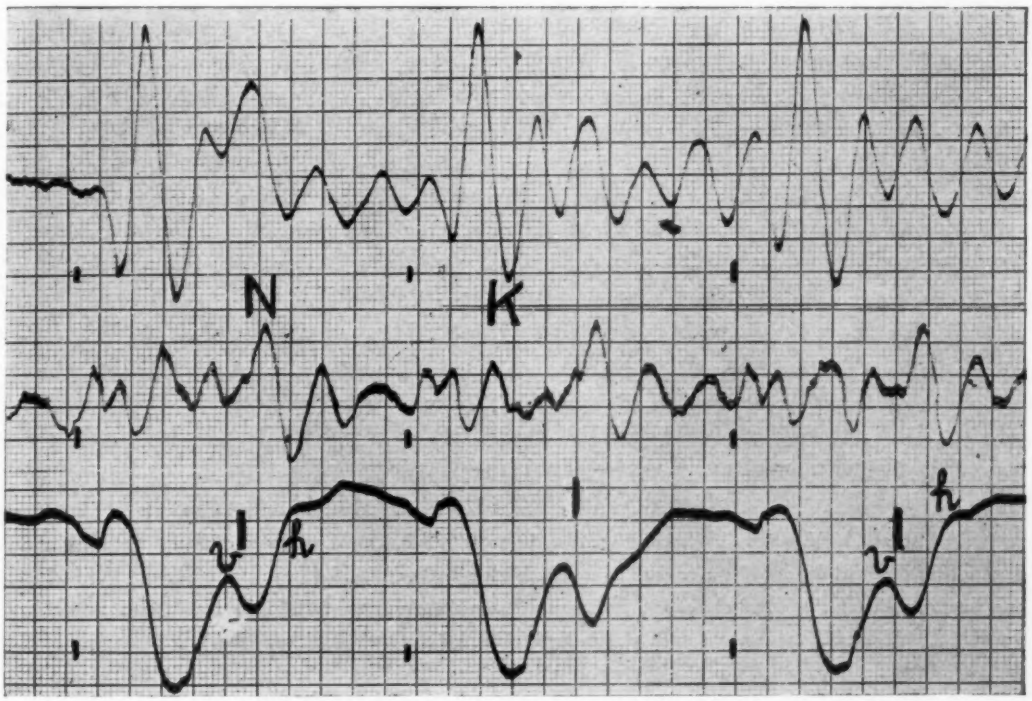

Fig. 1.—The head-foot ballistocardiogram (top), the lateral thoracic ballistocardiogram (center; rightward motion up), and jugular pulse of Mur, a 17-year-old lad, with a loud third sound occurring early (0.12 sec. after second sound). Small dots show the position of R waves, large black bars position of third sound, on traces taken simultaneously. Time in tenths and fiftieths of a second. The diastolic lateral complex is the largest associated with the third sound in any of the six subjects; the jugular *h* wave is typical of those seen in two other subjects, where the third sound occurred lower on the falling limb of *v*.

On a 4-channel galvanometer the electrocardiogram, three- plane ballistocardiogram,[23] apex beat, and apical heart sounds were recorded in various combinations. While using this instrument, the apical sounds, the electrokymograms of left border motion, and the jugular pulses of the four subjects with loudest third sounds were recorded. All pulses were recorded with a piezoelectric pickup, and the border motion with the Cambridge electrokymograph and a fluoroscope with full-wave rectification. In tabulation of the results we have adopted Hirschfelder's "h" to indicate the upward peak on the jugular pulse curve which follows v in early diastole. This is the same as Gibson's "b" wave, and probably the same as Bard's "f" wave.[24]

Checks for time lag between the phonocardiograph, the piezo pickup and tube to apex or jugular pulse, and the photomultiplier and amplifier for electrokymography, showed less than 0.02 sec. delay in the electrokymograph and in the apex recorder on the Cambridge instrument; less than 0.01 sec. for the piezoelectric and short tube pickup used with the Polyviso.

RESULTS

The ballistocardiograms in three subjects showed no consistent pattern of diastolic waves in any plane which could be related to the third sound. Two (Spo and Red) showed a leftward wave followed by a larger, slower, rightward one, with the third sound at or just before the rightward motion. These were consistent but small. In the lad with the loudest third sound (Mur), a rightward excursion began abruptly after the third sound, and this was followed by a leftward sweep (Fig. 1). This complex was the largest of the heart cycle in that plane, and is similar to those regularly seen in patients with gallop. The slit kymograms and electrokymograms of left ventricular border motion (Fig. 2) in five cases showed rapid early diastolic filling and broad diastolic plateaus in no way to be distinguished from those seen in mitral insufficiency, myocardial failure, or constrictive pericarditis when gallop is present. In all cases motion was greater at the base than at the apex, as is usual in supine (in contrast to erect) subjects.[25] In the sixth case (Sne), with no third sound when supine, the border showed a parabolic rise, with no sharp inflexion in early diastole, no plateau. This is the curve inscribed by most persons with no gallop or third sound. The fourth and fifth cases had inflexions less sharp than in those with louder third sounds. All five cases with clear third sounds showed sharp inflexions on the early diastolic rise of the apex impulse (Fig. 3). In the many sound records of these three youths only one showed, in the low-frequency records on the Polyviso, the small single oscillation which Luisada calls a normal opening snap. This is quite inaudible and can scarcely be called a "p f t," 0.04 sec. after the second sound.

In the four cases with the loudest third sounds, jugular pulse curves free of carotid elements were obtained in three (Fig. 1) and electrokymograms of the left auricular and left ventricular border motion (Fig. 2) were obtained in two of these three, simultaneously with electrocardiograms and apical phonocardiograms. The subjects were supine, left shoulders up at about 20°, and the third sounds were less intense and later than when the data in Table I were obtained. The following intervals were determined from these curves; jugular v peak to third sound, 0.03 sec. (range, 0.02 to 0.06); left auricular v peak to third sound, 0.09 sec. (range 0.08 to 0.10); third sound to trough between jugular v and h waves, 0.06 sec.; third sound to trough between left auricular v and h waves, 0.01 sec. (range, 0 to 0.02 sec.); third sound to jugular v-h trough, 0.06 sec.; third sound to left auricular h peak, 0.13 sec.; third sound to jugular h peak, 0.17 sec. The other data obtained from the six subjects are given in Table I. The interval from the R peak of the electrocardiogram to the onset of the second sound averaged 0.33 sec., with a range in all the tracings only from 0.32 to 0.35 sec. The second- third sound intervals in Table I are those

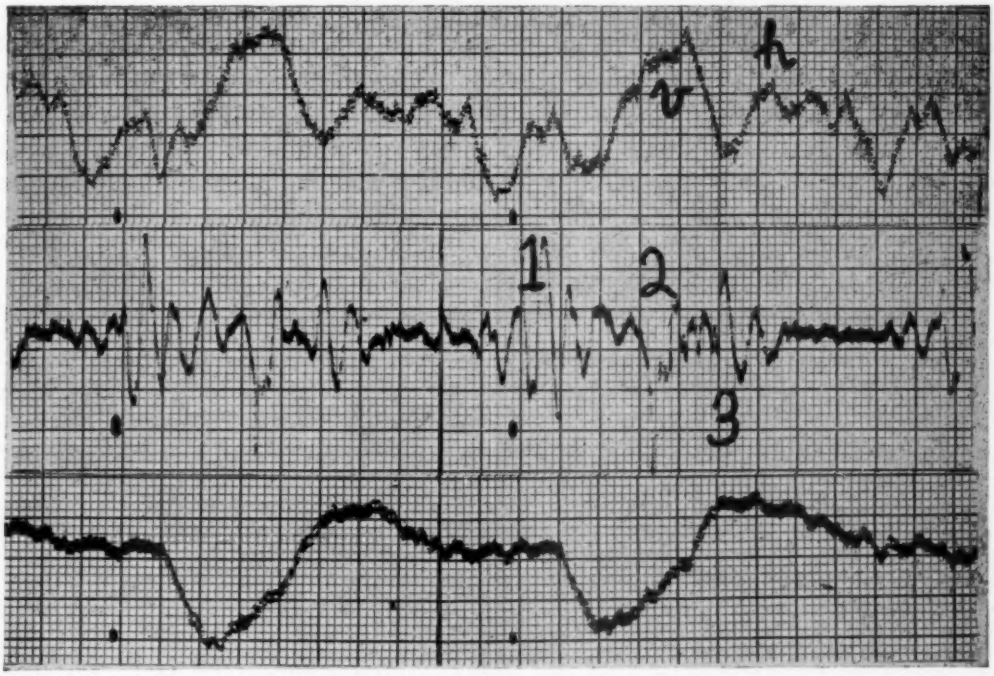

Fig. 2.—The electrokymogram of the left auricle (top), the left ventricle (bottom), and the heart sounds at apex (center). The position of R waves from the simultaneous electrocardiograms shown by black dots. The outward swing of the left border near the base of the heart begins 0.10 sec. before the second sound, but the inflexion on the expansion curve falls with the third sound. Same subject as Fig. 1, but third sound 0.14 to 0.16 sec. after second sound with patient supine and left shoulder and side elevated 20°. Note auricular downstroke before R wave. The trough between *v* and *h* is synchronous with the third sound.

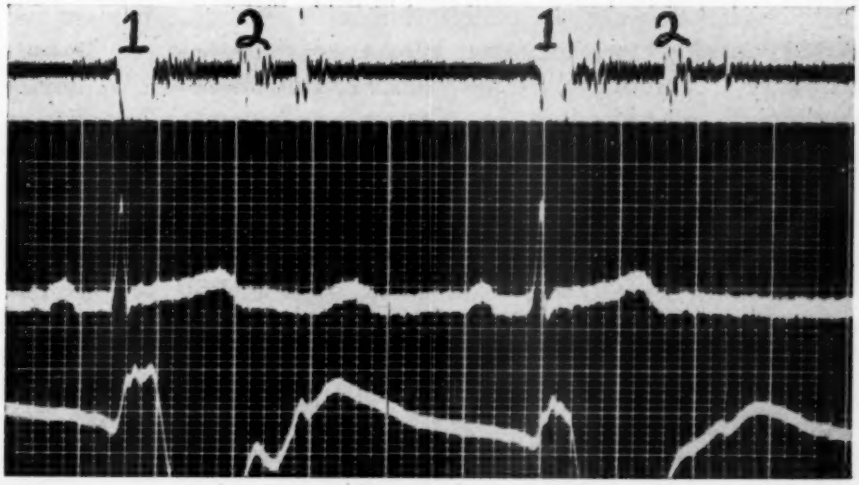

Fig. 3.—Heart sounds at apex (top), Lead II (center), and apex beat (bottom) from a 17-year-old lad (Men). The first cycle here is the third; the second is the sixth after breathing was suspended in mid-position. As the sound grew fainter, the rise at the apex after the second sound became smaller. Time in fifths and twenty-fifths of a second.

observed in the left lateral position, when the third sound records most closely approached the second sound in intensity. The third sounds were latest and faintest, in the records made with the electrokymograms, for here the subjects had the left side somewhat elevated and had held their breath for several heart cycles before the records were made. As seen in other tracings, this sound fades out when the breath is held (Fig. 3) and it varies during normal respiration.

TABLE I. RELATIVE INTENSITY* AND TIME RELATION OF THE THIRD HEART SOUND AND OTHER EVENTS IN THE CARDIAC CYCLE

NAME	INTENSITY OF THIRD SOUND			TIME INTERVALS IN HUNDREDTHS OF A SECOND				
	SUPINE	LEFT LATERAL	SITTING	2ND TO 3RD	L.V.T. TO 2ND	2ND TO A.T.	2ND TO L.V.P.	2ND TO A.P.
Mur.	0.5	1.	0	12	12	8	12	13
Spo.	0.5	0.5	0.2	13	4	2	14	15
Men.	0.3	0.5	0.25	15	10	10	16	16
Sim.	0.1	0.25	0.05	14	4	6	16†	14
Red.	0	0.1	0	16	7	5	15†	16
Sne.	0	0.05	0	18	10	5	—	—
Aver.	0.23	0.4	0.08	14.7	8	6.6	15.1	14.8

*Intensity given as ratio of third sound intensity to that of second sound, in same cycle, at the apex. L.V.T. is the end of the systolic inward motion of the left ventricular border in the slit kymogram; L.V.P. is the inflexion at the end of early diastolic outward motion of the left ventricular border. A.T. is the inflexion preceding the diastolic thrust at the apex; A.P. is the inflexion at the end of the thrust.

†Inflexion is not sharp.

DISCUSSION

It is somewhat sobering to realize that with the most modern methods, we can add nothing to the facts known to Barié[2] in 1893, or to the younger Chauveau in 1902.[26] We have more elegant methods; we have shown, as did Benjamin[10] and Luisada,[27] that the venous phenomena of gallop or third sound are evident on the left side of the heart as well as the right; and we, like Taubman and Brady,[13] and like Kuo and associates,[28] have followed the diastolic expansion of the left ventricle from apex to base. All this serves only to give precision to the confirmation of previous students. They correctly identified the relation of these protodiastolic sounds with the peculiar apical retraction and venous reflux which can be recorded in all such cases. None of these phenomena occur in patients with mitral stenosis, and we have confirmed the fact that the third sound falls in the same period as gallop, and averages 0.08 sec. later than the opening snap. Yet it is only fair to add that the latest snaps occur in cases with relatively low left auricular pressures,[29] and these sounds overlap the range of the earliest gallop and third sounds. Since this often occurs in young people with normal, or even small, hearts, the possibility of confusing snap and third sound is not remote. Apex tracings or slit kymograms can provide sure differentiation between the two conditions.

The Venous Reflux.—We can offer no explanation for Eddleman's curves in which the jugular v wave has its peak synchronous with the third sound, has a gradual descending limb, and is not followed by a sharp rise. Our Fig. 1 is quite typical of the findings of others, from Barié, Chauveau, Hirschfelder and Gibson with their crude polygraphs to Luisada[27] (his Fig. 58, p. 98), and to Sloan and associates[30] using the latest devices. The third sound falls from the middle third to the base of the descending limb of the jugular v, while the opening snap occurs just before or after or on the peak.[31] Ohm pointed out repeatedly that the waves of the jugular pulse represented cardiac events occurring 0.04 sec. earlier. Our curves show a delay of 0.04 to 0.06 sec. between left auricular events and corresponding jugular waves (Fig. 2). If the auricular v peak marks the beginning, and the sharp inflexion at the end of the descending limb of v marks the end, of early diastolic ventricular expansion, then all this confirms the view which Thayer[5] summarized when he ascribed the third sound to ". . . sudden tensing of the mitral, and perhaps at times of the tricuspid, valves at the *end* of the first and most rapid phase of diastole."

That the delay between left auricle and jugular is not due solely to transmission of the pulse wave is suggested by the report of two normal subjects in whom simultaneous right and left auricular pressure curves were obtained by catheter; in both cases the v peak of the left auricle preceded that of the right by 0.04 sec., as did the end of its descending limb.[32] Benjamin's[10] and Luisada's[27] (his Fig. 60a) curves of left auricular pressure, recorded from the esophagus in cases with third sound, show the v peak less than 0.05 sec. after the onset of the second sound, with the end of the descending limb preceding the third sound by 0.01 to 0.06 sec. On the other hand, both Luisada[27] (his Fig. 81c) and Anderson[33] found that electrokymograms showed that left auricular peaks and troughs occurred later than those of the right auricle. We would consider the sources of error in the latter study to be greater than in the pressure measurements. In a study of gallop in constrictive pericarditis, the right atrial pressure, recorded together with the electrocardiogram and phonocardiogram, showed a steep fall, beginning 0.02 sec. after the second sound, ending abruptly 0.01 sec. before the gallop sound, and rising sharply to the level of its v peak within 0.05 sec.[34]

The venous phenomena can be summarized, then, as differing from those in people with no audible gallop or third sound by showing a much sharper fall in early diastole, starting 0.01 sec. after the second sound when auricular pressure is abnormally high and no later than 0.10 sec. when it is normal. This fall terminates abruptly within 0.01 sec. of the third sound, and is followed by a sharp rise, lasting 0.05 to 0.1 sec., and with a plateau lasting up to auricular systole more often than a fall. In those with normal third sounds the jugular wave shows this pattern more often than in those with gallop due to myocardial failure. When the left ventricle fails, but systemic venous pressure is normal, the jugular waves may have the normal pattern seen in adults with no normal third sound, while in young people with third sounds the sharp fall and rebound of the jugular pulse is usually present.

The Inflexions on Curves of Early Diastolic Expansion of the Ventricles.—Since the time of Barié[2] all who have studied apical impulses or ventricular border motion have been impressed by the fact that in those with third sound or gallop there is a sharper early diastolic outward thrust than in those without these sounds, and that a sudden inflexion occurs at the end of this phase of expansion. Simultaneous records at the apex show that the inflexion and sound occur almost at the same instant, the inflexion usually occurring with, or no more than 0.01 sec. after the onset of the sound. As emphasized by Lewis and Dock,[11] and shown in their Fig. 4 and in our Fig. 3, in a given case the sharpness and size of the rise and the inflexion vary in parallel with the loudness of the sound, as the latter varies during the respiratory cycle.

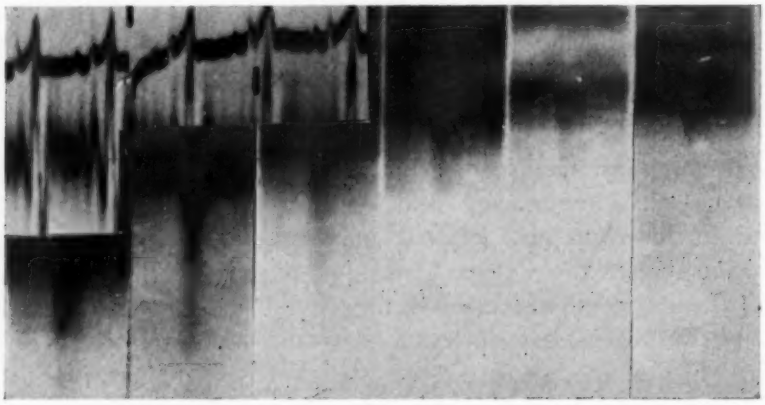

Fig. 4.—From the tricardiogram on the same subject as in Fig. 3. Five frames of left ventricular border, with base at the left side, and with electrocardiogram and ballistocardiogram as insert. The black bars mark instant of onset and offset of x-ray beam, seen as breaks in base line. Note diastolic plateau and decrease in size and duration of contraction and expansion in successive frames from base to apex. The lower edge parallels the vertical axis of the thorax.

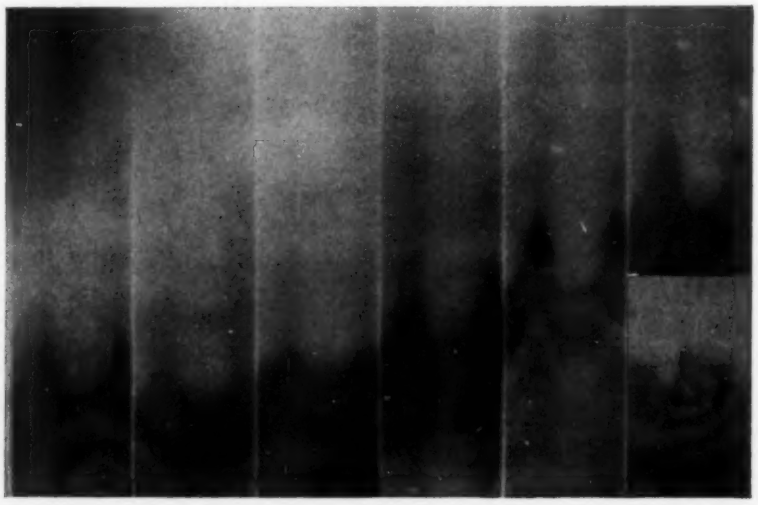

Fig. 5.—From the tricardiogram of subject Spo. Insert shows a frame at the level of the pulmonary artery. This subject had the largest excursions and most uniform pattern of left ventricular border motion. Diastolic expansion is almost as swift as systolic contraction.

The records made by roentgen techniques show that the convexity and base have more rapid outward motion in these cases than in normals. But the pattern and the time relations vary from point to point and only close to the apex can one regularly find a close relation in time between the third sound and the inflexion. When tracings are made on subjects in the erect posture, the base and convexity of the left ventricle move less than the apex, and inward motion of this area may continue past the second sound, while the apex is moving outward. In recumbent subjects, the convexity usually ceases inward motion and may move rapidly outward during the last quarter or third of systole. The extent of motion at the base is much greater than at the apex in recumbent subjects (Figs. 4 and 5), and the outward motion not only begins before the second sound, but it continues after the early apical inflexion and the third sound. At some points, there may be inflexions soon after the second sound in every cycle[13] (their Fig. 1) or in the cycles where the gallop sound is relatively faint[13] (their Fig. 3). In Kuo's experience the inflexion occurred always 0.02 to 0.04 sec. after protodiastolic gallop, and even later in some cases of presystolic gallop.[28] Fig. 4 of Brady and Taubman[13] shows the inflexion at the convexity 0.04 sec. after a very loud third sound, while a simultaneously recorded apex impulse shows a much sharper rise and sharper inflexion, the latter occurring with the onset of the sound. In the five subjects with easily recorded normal third sounds (Table I), the outward motion along the convexity at the base of the left ventricle began 0.08 sec. before the second sound, outward motion at the apex 0.07 sec. after that sound. However, in these normal hearts, the diastolic inflexion near the base occurred almost simultaneously with the third sound and the inflexion of the apex impulse (Table I and Fig. 2). As is apparent in Figs. 4 and 5, there is a flat top to the plateau which occupies the last two-thirds of the intersystolic interval in the slit kymograms of the left heart border of these five youths. In the electrokymograms the border appears to move mesially at this time (Fig. 2). This is a result of distortion due to condenser-coupled amplifiers in the circuit recording fluorescence.

The point of inflexion in the slit kymograms does not occur at the same instant at all points on the ventricular silhouette. The earliest inflexion was chosen in making Table I, and the time from the R peak to this point, minus the R-second sound interval in the supine posture, used to calculate the figure in the column "2nd to L.V.P." This is less than 0.01 sec. later than the inflexion at the apex, on the average. In none of these six cases was there as much variation in motion from one point to another along the left border, nor as much difference between the earliest sharp inflexion on the border and at the apex impulse as we have become accustomed to seeing in slit kymograms and electrokymograms of patients with gallop due to constrictive pericarditis or to myocardial failure.

The Ballistocardiogram in relation to the Protodiastolic Sounds.—In head-foot ballistocardiograms one not infrequently sees large L or N peaks which follow protodiastolic gallop, or large early H waves following presystolic gallop. A curve from this laboratory, previously published[35] (Fig. 54) shows that the height of the N wave varies in parallel with the intensity of the third sound

when such a gallop (due to rheumatic carditis) varied from beat to beat during the respiratory cycle, showing that this phenomenon, like the apical thrust and inflexion, is related in intensity as well as in time to the protodiastolic sound. These protodiastolic waves are regularly much more striking, and in many cases are only in evidence, in the lateral[36] or, more rarely in the dorsoventral ballistocardiogram. In cases of mitral or tricuspid insufficiency, a large footward, leftward, or frontward wave occurs just before the third sound, and the larger headward, rightward, or backward wave follows. In complete heart block large lateral waves occur after auricular systole, the principal wave, j, begins 0.20 sec. after the onset of P and sweeps to the right for 0.10 to 0.14 sec.[35] (their Fig. 126, p. 230). These waves prove that a vigorous rightward and headward force, sometimes associated with a diastolic heart sound, occurs at the end of a phase of rapid inflow to the ventricles.

In the six youths with third heart sounds and healthy hearts, two had small waves of this type but only one showed real "gallop waves." This was the lad with the loudest third sound (Mur; Fig. 1). Old men, with healed infarction or heart failure, often have "gallop waves" in the ballistocardiogram but no demonstrable diastolic sound. Most young men with audible third sounds have no such diastolic motion of the body.

The Mechanism of Protodiastolic Heart Sounds in Relation to the Venous Reflux, the Abrupt Cessation of Ventricular Expansion, and the Ballistocardiographic N Wave.—Our evidence confirms all but one of the many studies on relation of apex beat and jugular pulse to the third sound, namely, that the sound occurs at or very near the end of early and rapid inflow to the ventricles. This rules out the suggestions that the sound is due to flapping of valves, eddy currents, or rapid change in tension of the ventricular wall. For the heart is silent at the peak of the velocity of flow or change in form and tension in the ventricle; the sound occurs as all these fall to zero. Since the sounds have been heard and recorded[37] in intact and exposed hearts of dogs, it is unnecessary to consider the idea that the third, or any other heart sound, is due to impact on the thoracic cage.

Only two theories are compatible with the evidence of venous reflux and apical inflexion at the instant the sound occurs. One was clearly stated by Potain[38]: ". . . the dilating ventricle quickly reaches the point where the fibrous resistance of its wall limits its distention, and the latter, sharply arrested, causes a tension, a shock and the gallop sound." Ohm,[15] who reintroduced this theory, took the jugular reflux as evidence of a sharp resistance to ventricular distention, which was the cause of "a backward movement, which requires a certain time (0.04 sec.) to appear at the jugular." This theory has been accepted by the great majority of subsequent students, including Kuo and his associates,[28] who noted in their electrokymograms that outward motion was not arrested at the moment the third sound occurred. If one accepted these records of border motion as valid representations of volume change of the ventricles, it would be logical to reject Potain's theory, for the ventricles thus examined seem not to have reached a limit of distensibility when the sound is recorded. Since they also seem to begin to distend as much as 0.10 sec. before

the second sound, in records made from the left border above the apex, it is obvious that it is impossible to assume that motion of the roentgen silhouette of the convexity or base does accurately represent change in ventricular volume. If one accepts the motion of the apex as the best index of the onset and end of inflow, it is possible to accept Potain's theory.

Having studied border motion with the roentgen cinematograph, the slit kymograph, and the electrokymograph, in erect and recumbent subjects, we have repeatedly seen that "rounding out" of the heart causes the lateral wall to move out of phase with the apex. In recumbent subjects it moves outward before systole ends. After a period of rapid inflow has stretched out the heart, it again may round out so that the lateral border moves out for a few hundreths of a second after the apex begins to move inward. This occurs after blood in the auricles has ceased to move into the ventricles. Therefore, the theories of Potain and Ohm are quite compatible with the evidence obtained by subsequent studies, including this one, for the expansion of the left ventricle does stop precisely at the moment the sound occurs. Indeed, in the healthy heart, this is more evident than in distended and failing hearts, where rounding out is more marked and lateral motion near the base lasts longer after the third sound. But the most convincing proof of Potain's theory is the study of a case of constrictive pericarditis reported by Kuo and his colleagues in 1951.[34] Here there was a "fibrous resistance," provided by the dense pericardium, and the fast early diastolic rise at the apex and fall in right intra-auricular pressure ended precisely at the instant the third sound began.

However, this evidence is equally compatible with the thesis propounded by Hirschfelder,[7] by Gibson[8] and by Thayer.[5,6] Reflux toward the veins is the only possible explanation for the sharp rise in intra-auricular pressure,[34] in jugular pulse, and in left auricular volume which begins immediately after the third sound. This in turn must be due to a preceding and sustained rise of the A-V septum, that is, of the leaflets. That such a rise occurs at the end of rapid inflow to the ventricles, as shown by Henderson in 1905, has been confirmed by more refined cinematographic methods of study.[39,40] Gibson in 1907 stated that ". . . with a rapid and full stream the tightening of the valves would be quick and strong, while with a slow stream it would be gradual." All the evidence so far collected shows that the loudness of third sound or gallop varies with the rapidity of inflow and of reflux. If these sounds were limited to cases of constrictive pericarditis, and our studies were limited to records of motion or pressure in the heart chambers, it would be impossible to choose between Potain's theory and Gibson's.

But in myocardial failure and in normals with third sounds, there is no evidence that any "limit of distensibility" has been reached when the sound occurs. These subjects, like those with no diastolic sounds, show a great increase in ventricular volume when the arterial pressure peak is reached during rebound from the Valsalva maneuver. It appears that much of the misunderstanding of this sound is due to the use of the term "ventricular filling," instead of what the Continental writers, like the Greeks, mean by "diastole," namely, ventricular expansion. At the end of rapid inflow, in myocardial failure, the

ventricle is not full, and increase in severity of failure may lead in a few hours to a further marked increase in diastolic volume. It simply is not true that an inflexion on the ventricular diastolic volume-pressure curve has been reached when third sounds occur. It must be realized that "cessation of inflow" is not the same as "filling to capacity" in hearts with no fibrous pericardial or subendocardial constriction.

In studies on the changes in form and volume of the heart chambers of dogs, made with cinefluorographic angiocardiography, Rushmer and Crystal[41] discovered that the areas of the shadows cast by the ventricular chambers "remain relatively constant during the last two-thirds of diastole" (that is, of the whole intersystolic interval), "even in the presence of retrograde flow into the inferior vena cava", and even though the "diastolic volumes vary from cycle to cycle." A student of third sound feels safe in ascribing "retrograde flow" to the same force which keeps the jugular pressure rising sharply for as much as 0.2 sec. after the third sound. This can be ascribed only to Gibson's "quick and strong" closing of the A-V valves and rise of the A-V septum into the auricles. This is the force which causes reflux into the great veins and prevents further filling of the heart.

In normal dogs, the third heart sound is also heard and certainly is accompanied by the usual phenomena. And in normal men, third sounds occur in cycles in which the diastolic volumes vary from cycle to cycle, and yet hold a plateau after the third sound in each cycle. In the dogs studied by Rushmer and Crystal, and in many of our cases of gallop studied by slit-kymography, the heart expanded in early diastole faster than it contracted in systole. This means that the entire mass of blood in the auricles and great veins moved toward the ventricles with considerable force. Unlike the blood expelled from the ventricles, this mass of blood can not expend its energy in flowing onward. The mass of blood pressing out the flaccid ventricular walls is constantly being decelerated, and when the energy stored in the distended veins has been fully utilized, the wave entering the ventricles is reflected, and the concave wall focuses this reflected energy on the auriculoventricular orifice. Thus the valves are closed, auricular pressure rises sharply, and a wave sweeps back through the great veins. In gallop, where the mass of blood in the over-distended veins is great, and the energy of the stretched fibers is two or three times normal, the inertia of this reflected wave is sometimes greater than that of the blood ejected by ventricular systole. Then the headward, rightward or dorsalward motion of the thorax recorded by the ballistocardiogram, following the gallop sound, exceeds the motion inscribed during systole. The fact that the sharp ballistic wave which follows immediately on the third sound always is directed rightward, headward, or backward surely means that the force released by the wave of reflux is more concentrated and powerful than that which acted during ventricular filling.

That a wave of such force, moving from the ventricle toward the great veins, can suddenly draw taut the A-V valves and evoke a sound approaching, or at times, exceeding the first sound in intensity is not surprising. Recent evidence on the relation of time of onset of the first sound to left auricular pres-

sure has shown that the first sound does not necessarily occur when systolic contraction has raised tension of left ventricular fibers to some specific level; it occurs only when ventricular pressure rises above that in the auricle and forces the valves upward, tautening their fibers.[29] This, with older evidence on the relation of first sound intensity to early diastolic or auricular systolic inflow, leaves little doubt that the audible vibrations of the heart sounds arise almost exclusively in the fibers of the valves and the roots of the great vessels, not in the thick jelly of the ventricular walls.

By closing the nasopharynx and lips and forcibly exhaling, we can swiftly and fully distend our cheeks, which have the thickness and structure of ventricular wall. No sound is produced. Even if we touch these distended cheeks with our finger tips and raise pressure suddenly by pressing inward, no sound is produced until air is forced from our lips. If we grasp the edge of the lower lip, draw it away from the teeth slightly and dry the fold, forceful tugs on the lip cause no sound. Yet a strip of cloth held in the teeth and tugged taut with equal force causes a sound like a heart sound. Hence, it is unlikely that even a potentially "musical" structure like the pericardium will emit a sound when drawn taut if it is fused with the ventricle wall, or that a drum head will give off familiar sounds if covered with a layer of raw meat an inch thick.

There are, then, three main objections to the theory that the third and gallop sounds arise in tensed ventricular walls. There is no evidence of tensing of these walls except in constrictive pericarditis; there is no evidence that audible sounds can be evoked by suddenly tensing structures like the lips, cheeks, or ventricles, and there is ballistocardiographic evidence that the force acting on the thorax at the moment the sound occurs is directed not from auricle to ventricle but in the opposite direction. On the other hand all the evidence is compatible with Gibson's thesis that third sound and gallop are due to tensing of A-V valves by reflux after a rapid inflow of blood, and with the view of Barié that gallop sounds are "an exaggeration of that which occurs in every one, without causing a perceptible noise."

While the rapid inflow, the apical inflexion, the jugular reflux, and the plateaus on the curves of lateral border motion of those with normal third sounds and those with gallop are quite comparable, in time of occurrence and range of magnitude, the ballistocardiographic motion associated with gallop, especially in the lateral plane, is very much greater than that encountered in those with a third sound. Indeed, except in those with the loudest third sounds, such waves are usually absent when all the other features common to the two conditions are present. This, we believe, is due to the fact that the quantity of blood set in motion in the dilated veins of those with heart disease, and the end-systolic tension in these veins, is far greater than in the normal young people who have third sounds. The latter have hearts which relax swiftly, and resilient elastic veins which, even at normal venous pressures, can expel their contents rapidly in early diastole. This suffices to set in motion the ventriculovenous reflux which prevents further ventricular filling for that heart cycle. In these young people, there is no change in the slope of the curve obtained by plotting ventricular volume against pressure at the moment inflow ceases. Even

in myocardial failure there is no sharp limitation of expansibility at the time gallop occurs. In constrictive pericarditis there is a sharp change in the slope of the pressure-volume curve as the pericardial capacity is reached in early diastole, and similar inflexions of the curve probably occur with fibroelastosis.

One recent report ascribes the third sound of normal subjects, and of cases of myocardial failure, as well as that of constrictive pericarditis, to tensing of the pericardium.[42] This was based on a comparison of the wave forms of this sound in constrictive pericarditis with the forms in the other groups, and on the assumption that in the former the sound must come from the dense membrane. These authors were unaware of the fact that it is in cases of constrictive pericarditis that evidence for reflux is most striking: sharp rises in auricular and jugular pressure, huge rightward and headward ballistic waves having been reported in most cases in which these phenomena have been studied[34,36] (and in all cases of this disorder whose jugular pulses and three-plane ballistocardiograms have been recorded in our laboratory).

In constrictive pericarditis, as in other cases with gallop or normal third sound, the diastolic sound closely resembles the first sound. This is clearly shown by the high-speed records of the heart sounds of one of the cases reported by the group who ascribed the sound to "tensing the pericardium"[42] (their Fig. 1). There is nothing in the frequency, intensity, or duration of the third sound in pericarditis to indicate it arises in a dense and heavily damped membrane, such as the diseased pericardium, and there is now overwhelming evidence that this sound, and the audible vibrations of the first sound near the apex, arise in suddenly tensed auriculoventricular valves.

SUMMARY AND CONCLUSIONS

1. Graphic registration of events associated with the third heart sound and protodiastolic gallop have been reported repeatedly over the last sixty years, and all but one recent report agree in showing that these sounds occur at the very end of the rapid inflow to the ventricles, and that they are associated with an apex thrust and rate of fall of venous pressure greater than those of other people, or even of the same people in other heart cycles, when there are no such sounds.

2. Roentgen studies of the left-heart border in those with third sounds and gallop show that the ventricular expansion is completed about at the time the sound occurs. Because of "rounding out" of the heart, the border near the base may continue outward motion for 0.04 sec. or more after the maximum volume has been reached and apical retraction has occurred.

3. The present study, on six young men, confirmed these facts and showed once more that the intensity of the normal third sound varies during the respiratory cycle and with posture. The sharpness of the apical thrust and of the jugular reflux vary in parallel with the intensity of the sound.

4. Only with the loudest third sounds is there evident the headward or rightward thrust of the body, shown in ballistocardiograms, which is so striking an accompaniment of most gallop sounds from diseased hearts.

5. The direction of this wave shows that the force causing the sound is acting, not from auricle toward the ventricle, as would be the case if the sound

was due to tensing the ventricular walls, but in the opposite direction. It is also pointed out that only in constrictive pericarditis is the heart in a condition of altered distensibility when the third sound occurs, and that the normal hearts of men and dogs may show constant volume for the latter two-thirds of diastole even when this volume varies from cycle to cycle with respiration.

6. Because the valves are certainly drawn taut at the moment reflux begins, after rapid inflow ceases, and because the valves are structures easily set into audible vibration, while the flabby ventricular wall is not a suitable structure for emitting sounds, it is concluded that the third sound and gallop sounds originate when the auriculoventricular valves are forcibly tensed by a reflected wave.

7. The earliest gallop or third sound falls at the same time in the heart cycle as the latest opening mitral snaps. With the latter, there is no rapid rise of the apex, sharply inflected with the sound, and the ventricle expands slowly, not unusually fast, as with normal or pathologic third sounds. As a general rule, normal third sounds vary widely during each respiratory cycle, while opening snap and gallop vary but little from one heart beat to another. Small or normal-sized hearts, in cases of constrictive pericarditis or mitral stenosis, may be associated with third sounds 0.12 sec. after the second sound, which in graphic records of single cycles are indistinguishable from normal third sounds, but records made during normal breathing, with apex impulses, usually make it quite evident whether we are dealing with an opening snap, a gallop, or a normal third sound.

SUMMARIO IN INTERLINGUA

Esseva registrate in varie combinationes sonos cardiac, pulsos jugular, impulsos apical, fissikymogrammas, electrocardiogrammas, e ballistocardiogrammas triplanar in 6 juvene homines con varie grados de intensitate del tertie sono cardiac. Nos conclude que le tertie sono occurre simultaneemente con le abrupte termination del expansion ventricular al comenciamento del diastole e le initiation del refluxo verso le duo auriculos quando le unda del influxo es retroflectite contra le orificios auriculoventricular. Le sono es debite al resultante tension valvular, de accordo con le prime interpretation offerite per Gibson, Hirschfelder, e Thayer in 1907.

Durante que le galopo protodiastolic ha un simile origine e occurre al fin de rapide influxos, illo es regularmente accompaniate per un forte unda ballistocardiographic verso le capite e le latere dextere. Iste phenomeno occurre in individuos normal solmente in le presentia de un fortissime tertie sono.

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Clinical Reports

CONGENITAL ABSENCE OF THE LEFT PULMONARY ARTERY

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INTRODUCTION

THE increased awareness of congenital vascular abnormalities and the more widespread use of angiocardiography have resulted in the clinical diagnosis and reports of three cases of congenital absence of a main pulmonary artery in the past two years. This is a marked contrast to the preceding 100-year period during which only nine cases were recorded in the literature, all having been diagnosed at autopsy or during surgical exploration.

We wish to report an additional case, originally suspected on clinical and routine roentgenologic examinations and later confirmed by angiocardiography.

CASE REPORT

R. R., a 21-year-old white male, reported sick on October 20, 1953, because of an acute upper respiratory infection with associated cough. Because of these symptoms he was referred to the hospital for a chest x-ray. A 70 mm. photoroentgenogram was taken which demonstrated marked radiolucency of the left lung. The patient was therefore requested to return for further radiographic examination of the chest. As a result of this routine roentgenologic examination, a diagnosis of probable atresia of the left pulmonary artery was made, and the patient was then admitted to the hospital for further evaluation.

Careful questioning upon admission revealed the following significant features in the past history. At the age of 14 months he developed pneumonia involving the left lung which was complicated by empyema, necessitating surgical drainage. This illness extended over a period of three months. Chest x-rays were taken at that time, and no unusual abnormality was suspected. Subsequently, at the ages of four years and seven years he experienced uncomplicated attacks of "pneumonia," again involving the left lung. Although his growth and physical development were considered normal by himself and his family, throughout childhood and until the present time, his exercise tolerance had never been equal to that of others his age. For this reason he did not participate in the usual school athletics. In 1942, he underwent an appendectomy without complications. In December, 1951, he successfully passed a physical examination, including chest fluoroscopy, for employment with a large midwestern life insurance company. In February, 1952, he was drafted into the Army following an induction physical examination, including a chest x-ray, which reported no apparent abnormality. Throughout basic training the patient was handicapped by considerable impairment of his exercise tolerance and could never successfully complete the obstacle course. During his 15 months' tour in Germany prior to hospital admission,

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he performed the duties of a supply clerk without difficulty. Aside from the aforementioned three pneumonic episodes and the decreased exercise tolerance, the patient had not suffered from other significant symptoms such as cough, chest pain, hemoptysis, or sputum production.

Family history was entirely nonrevealing. Mother, father, and two brothers had no history of pulmonary or cardiovascular disease. The patient had smoked a package of cigarettes daily for several years without untoward effects.

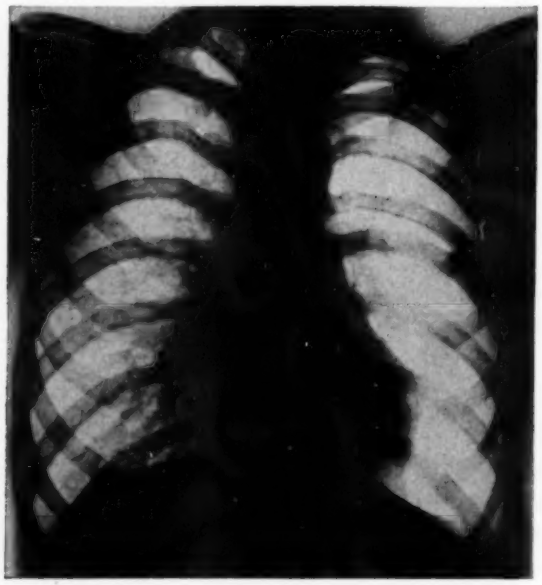

Fig. 1—Conventional posteroanterior roentgenogram showing absence of the left hilar shadow with diminished vascular markings and narrowing of interspaces over the left hemithorax.

By the time the patient was admitted to the hospital he had recovered from his acute respiratory illness and offered no complaints. He was a thin, muscular white male who was not dyspneic at rest. Temperature, 97.4°F.; pulse, 96; blood pressure, 110/84 mm. Hg; weight, 142 lb. Eye, ear, nose, and throat examinations were negative. No significant lymphadenopathy. The chest was asymmetrical with decreased fullness of the left hemithorax. There was a small well-healed linear scar at the ninth intercostal space in the left posterior axillary line, resulting from the childhood surgical empyema drainage. There was decreased expansion of the left thorax with moderately diminished tactile and vocal fremitus over the entire left lung field. Breath sounds were also appreciably diminished over the entire left lung field. The area of cardiac dullness was shifted slightly to the left. Heart sounds were normal with regular sinus rhythm and no thrills or murmurs. The second pulmonic sound was equal to the second aortic sound. The abdomen was soft with no palpable organs or masses. There was no clubbing of the fingers or toes. The remainder of the physical examination was within normal limits.

Laboratory data: Routine urinalysis negative. Hemoglobin, 16.0 grams. Hematocrit, 54. Red blood count, 4.82 million. White blood count, 9,500 with normal differential. Sedimentation rate, 2 mm./hr. Cardiolipin microflocculation, negative. An electrocardiogram revealed vertical electrical position of the heart without unusual rotation of the electric axis. Arm-to-lung circulation time, 5 seconds. Vital capacity, 3,100 c.c.; predicted normal, 5,400 c.c.

Chest x-ray (Fig. 1) revealed the left hemithorax to be smaller than the right with narrowing of the intercostal spaces and a marked increase in the radiolucency of the entire left lung. The usual shadow of the left main pulmonary vessel was not visible, and there was a generalized diminution of vascular markings on the left lung field. The heart and mediastinum were shifted slightly to the left. Both diaphragms were normal in position. Chest fluoroscopy confirmed the absence of the left hilar shadow and revealed normal diaphragmatic excursions with no mediastinal shifting with respiration.

In view of the history and the abnormal physical and radiological findings, a congenital absence of the left pulmonary artery was suspected. It was felt that further studies were indicated to confirm this opinion. Bronchoscopy was performed and revealed a generalized diminution in the caliber of the visible left bronchial tree. Angiocardiography was performed with film exposures being made at 4 and 6 seconds (Fig. 2), confirming the absence of the left pulmonary artery.

The patient remained asymptomatic and was discharged after the completion of the diagnostic studies on the twelfth hospital day. Six weeks later, just prior to his return to the United States for discharge, the patient was re-examined and no additional findings were noted.

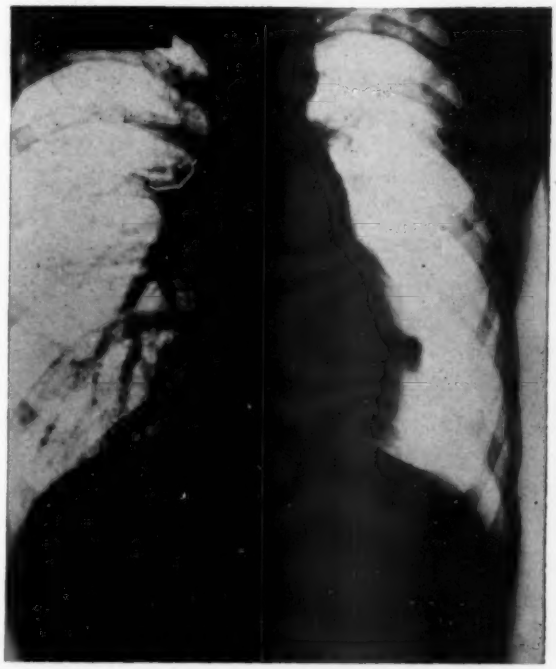

Fig. 2.—Angiocardiogram taken 4 seconds following Diodrast injection showing visualization of the right pulmonary artery and absence of the left pulmonary artery.

COMMENT

The literature contains twelve previously reported cases of unilateral congenital absence of a main pulmonary artery. The first case was reported by Fraentzel[1] in 1868 as an incidental autopsy finding in a case associated with multiple congenital cardiac anomalies. The following five[2-6] cases were diagnosed at autopsy and were all in infants with the exception of Müller's case[3] which occurred in a 35-year-old female who died of puerperal sepsis. All of the aforementioned cases were associated with serious congenital cardiac malformations. Blalock[7] in 1947 first reported the ante-mortem diagnosis of an absent left pulmonary artery as an incidental finding in a patient who underwent surgery for pulmonary stenosis. Following this, two additional cases were reported: one at autopsy,[8] and the other at operation.[9] Madoff and associates[10] reported the first clinically diagnosed case in a 14-year-old female. This case was confirmed by angiocardiography. Subsequently, Steinberg and associates[11] reported two

additional cases, suspected clinically and confirmed by angiocardiography. Nadas and associates[12] have recently reported three cases of atresia of the left pulmonary artery in children associated with tetralogy of Fallot. They reported an additional case with dextrocardia and tetralogy of Fallot which showed atresia of the right pulmonary artery. To our knowledge, this is the fourth case of absence of a pulmonary artery to be proved without resorting to exploratory thoracotomy or autopsy examination.

The diagnosis may be suspected from an analysis of the routine postero-anterior chest roentgenogram. Pertinent findings are a decrease in the size of the involved lung field combined with a marked increase in radiolucency due to the absence of the pulmonary arteries and the blood normally contained within them. The thoracic cage on the side of the pathology may be smaller due to underdevelopment of the lung. Mediastinal shift to the side of pathology is usually noted. In this case the diaphragmatic leaf on the abnormal side was normally situated. These x-ray findings are indeed highly suggestive of absence of the pulmonary artery; however, contrast studies of the pulmonary vasculature are necessary for an unequivocal diagnosis. Such a study should demonstrate contrast media in the pulmonary vasculature of the normal lung but no media in the abnormal appearing side.

We utilized routine angiocardiographic technique with the two-film exposure method. The early studies of Robb and Steinberg[13] indicated that visualization of the pulmonary vasculature could be successfully accomplished in this manner. Exposures were made 4 and 6 seconds following the injection of 60 per cent Diodrast, and both films demonstrated good contrast delineation of the pulmonary vasculature on the normal side but no visualization of the abnormal appearing left lung.

Our case demonstrated several interesting features of this condition. Outstanding is the minimal symptomatology which these patients may display. This patient had experienced three previous episodes of pneumonia involving the lung with the absent pulmonary artery; nevertheless, he showed only minimal physical incapacity. In fact, he was able to complete two years of active military service without significant loss of time from duty. The lack of significant pulmonary symptoms correlates well with findings in the five other cases diagnosed ante mortem. However, none of the previous case reports mentioned episodes of pneumonia in the clinical history. This case also points out how easily this diagnosis can be overlooked. In this instance, the patient had had several x-rays as a child because of recurring pneumonic episodes and in addition had within the past two years undergone two complete examinations, including, both times, a roentgenologic examination of the chest with no apparent abnormality being noted. This would lead one to suspect that there are probably other undetected cases in the general population. One case of Steinberg and associates[11] had been discharged from the Navy six years previously because a routine chest film showed " . . . that the right lung was pushed towards the heart." In our case it was a 70 mm. photoroentgenogram which first made us suspect this diagnosis and led to the eventual confirmation by angiocardiography.

Although there are no pathognomonic abnormal physical findings, our patient presented fairly pronounced abnormalities consisting of impaired chest expansion and markedly decreased breath sounds on the involved side without impairment of percussion resonance. This combination of physical findings should arouse one's suspicion regarding this condition, but in the long run the clinician must rely on the conventional posteroanterior chest film to suspect the diagnosis. Although complete pulmonary function studies and cardiac catheterization would have been desirable in this patient, they were not accomplished due to the fact that he was studied in an overseas Air Force hospital where the necessary equipment was not available.

We realize that this patient probably has an anomalous blood supply to the involved lung, since such a blood supply has been demonstrated in nine of the ten autopsied cases and in both of the cases diagnosed at surgery. It was our opinion that no surgical therapy was indicated in this case. Since this patient has had three separate bouts of pneumonia on the affected side, it is possible that the patient will have repeated infections on this side in the future. If this should occur, pneumonectomy might then be considered. Another potential complication in this condition is pulmonary hemorrhage. This has been reported in two previous cases[4,9] and might be another indication for surgery. A final indication for definitive surgery as Findlay and Maier[8] have suggested is the development of cardiac failure due to a large arteriovenous shunt through an anomalous arterial blood supply to the involved lung. In such a situation, ligation of the anomalous vessels or pneumonectomy might prove curative. Our case showed no evidence of congestive failure and we feel that the lack of progressive cardiorespiratory symptoms over a period of years makes this unlikely in the future. The increased likelihood of recurrent lung infection appears to us to be the greatest danger to longevity in this case.

SUMMARY

A case of congenital absence of the left pulmonary artery in a 21-year-old Army private is reported from an overseas Air Force hospital.

The diagnosis was suspected on a routine 70 mm. photoroentgenogram and confirmed by the use of a two-exposure angiocardiogram. The signs, symptoms, diagnostic criteria, and possible role of surgical therapy are discussed.

SUMMARIO IN INTERLINGUA

Es reportate le caso de un congenite absentia del sinistre arteria pulmonar observate in un simple soldato de 21 annos de etate a un del hospitales de ultramar del Fortias Aeree del Statos Unite.

Le diagnose esseva conjecturate super le base de un routinari photofluorogramma a 70 mm e confirmate per medio de un angiocardiogramma a duple exposition. Es discutite le signos, symptomas, criterios diagnostic, e le possible rolo de therapia chirurgic in iste caso.

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EISENMENGER'S COMPLEX ACCOMPANIED BY DOUBLE SUPERIOR VENAE CAVAE, THE LEFT DRAINING INTO THE LEFT ATRIUM

Report of a Case With Fatal Outcome Due to Vagus Irritation During Heart Catheterization

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THE simultaneous occurrence of two or more malformations of the heart and/or the great vessels is comparatively common. There is also a wide variability among the different types of combinations.

The occurrence of two superior venae cavae is not rare. The left-sided caval vein as a rule disappears in the sixth fetal month, being a remnant of the left ductus of Cuvier. A persistent vein may enter the right atrium, or empty into the right caval vein, or it may enter the arterial side of the heart into the left atrium near the entrance of the pulmonary veins. Dohn[1] considers the persistence of the left vena cava as " . . . probably the most frequent anomaly of the large veins." Chouke[2] in 1939 found 205 cases in the literature, and later several additional cases were reported. The frequency rate of double venae cavae probably is somewhere in the neighborhood of once in 700 autopsies (McCotter,[3] Sanders[4]). Double superior venae cavae also have been reported in connection with other anomalies, as for instance double azygos veins (Prows,[5] Sanders[4]); patent ductus arteriosus (DeGroot,[6] Lam[7]), and coarctation of the aorta (Brown[8]).

Since Eisenmenger[9] in 1897 described the multiple anomaly of the heart that since then carries his name (i.e., high ventricular septal defect, over-riding of the aorta, and right ventricular hypertrophy), many cases have been reported. The syndrome regained a new interest in the area of heart operations, because of the important differential diagnosis against the tetralogy of Fallot. Also in cases of Eisenmenger's complex a large abundancy of accompanying anomalies have been reported: patent ductus arteriosus, patent atrial septal defect, hypoplasia of the aorta, right-sided aorta, abnormal distribution of the coronary vessels, anomalies of the vessels leaving the aortic arch, patent foramen ovale, aneurysm of the aortic valves, retraction of the right aortic cusp, and coarction of the aorta (Bond[10]).

In the literature we have not been able to find a case similar to our own.

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CASE REPORT

A 10-year-old girl was admitted to the Department of Thoracic Surgery in Malmö (Thx 210/54). There were several cases of cystic kidneys in the family history, otherwise nothing of special interest. A systolic murmur had been observed one week after birth. Cyanosis appeared early, first being intermittent and later growing permanent. At 5 years of age she suffered from some severe fits of intense cyanosis and unconsciousness, some of these appearing in connection with an intoxication by laburnum flowers. Similar fits were reported to have occurred later, especially if she were scared or otherwise emotionally aroused. Gradually she became progressively disabled, not being able to walk longer than 10 meters without rest. She was comforted in the squatting position, which she took up as often as possible, provided nobody seemed to observe her.

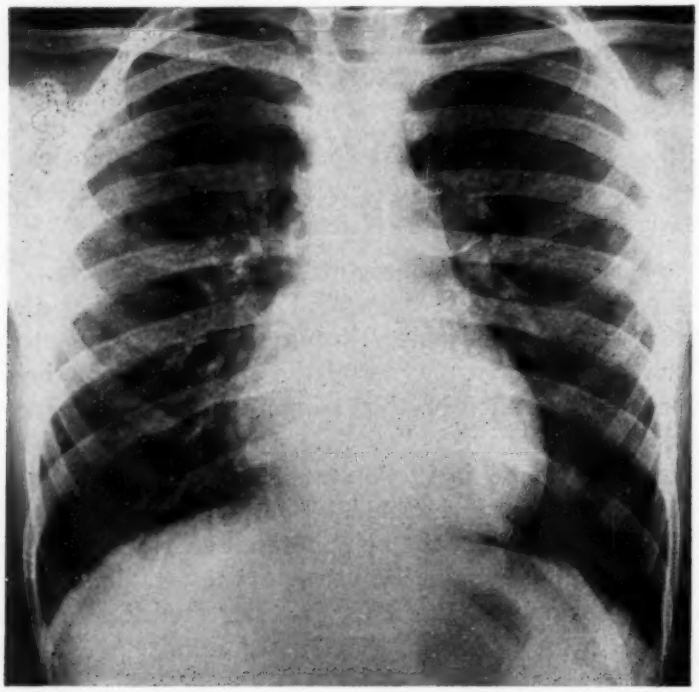

Fig. 1.—X-ray picture of the chest.

The *physical examination* revealed a thin but otherwise well-built girl, weighing 27.3 kilograms. The mental development corresponded to the age. She had marked clubbing of fingers and toes. Cyanosis was marked even in rest, especially in the lips, ears, fingers, and toes. She had slight dyspnea which became prominent on even light exercise. On auscultation a proto-diastolic murmur was heard in the third and fourth left intercostal spaces, and a weak systolic murmur in the third left intercostal space. The second pulmonic sound was markedly accentuated. Blood pressure was 130/80 mm. Hg. Hemoglobin was 19.2 grams per 100 c.c. and red cell count 6.1 ml./mm.^{3}

X-ray examination showed a somewhat enlarged heart with a heart volume, calculated to 385 c.c. per square meter body surface (according to the method of Kahlsdorff). Aorta was normal. The pulmonary artery as well as its branches was not enlarged and the hilar vascular shadows were at least not increased (Fig. 1).

Electrocardiographic examination: There was a regular heart action of 88 beats per minute. P-Q interval was 0.14 sec.; QRS, 0.07 sec.; T_1 to T_3 upright. S-T was elevated in Leads I and II, normal in Lead III, and chest leads. There was a marked right-axis deviation.

For further investigation the patient was referred for heart catheterization and selective angiocardiography.

Heart catheterization: After sedation of the patient with Pentothal sodium per rectum, the catheter was introduced into the left medial cubital vein. It was easily passed into the right side of the heart, reaching the right atrium. It was, however, not possible to pass the catheter into the right ventricle. It was then withdrawn and during a new attempt to reach the heart the catheter from the subclavian vein entered into the fluoroscopic projection of the left pulmonary field, apparently into an anomalous superior caval vein. In close connection with the passing of the catheter into this vessel the patient suddenly vomited and had a respiratory standstill. The airways were immediately cleansed by suction in the Trendelenburg position. After a few minutes, during which she had shown no signs of spontaneous breathing, the heart suddenly stopped. In spite of vigorous efforts of respiratory and cardiac resuscitation she died within a few minutes.

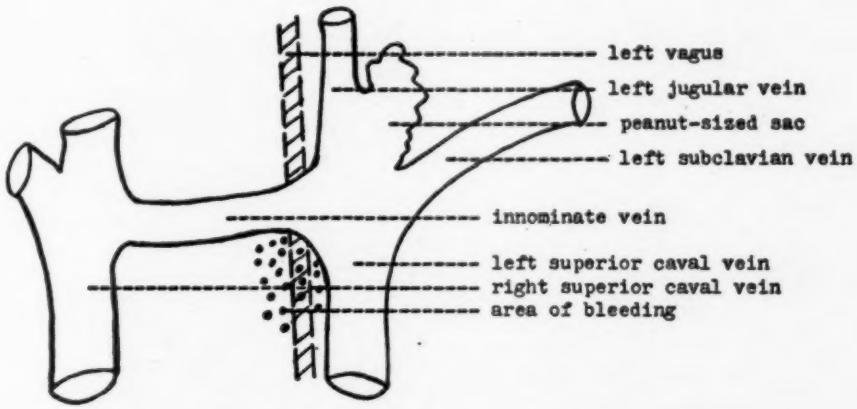

Fig. 2.—The anatomy of the upper chest veins, the vagus nerve, and the aneurysmatic sac in the reported case.

Autopsy: Post-mortem examination revealed a double superior vena cava, the left one leaving the junction of the left subclavian, left jugular, and innominate veins (Fig. 2). The anomalous caval vein entered the left atrium close to the left auricle. The diameter of the vein was 7 mm., equal in size with the regular right-sided caval vein. At the insertion of the left jugular vein into the junction of the subclavian and innominate veins there was a peanut-sized sac, resembling a badly developed heart auricle. Near this junction there was a small subintimal hemorrhagic lesion and just behind this lesion the left vagus nerve passed downward through a small limited area of bleeding connective tissue. There was, however, no sign of perforation.

The heart was enlarged showing a marked right hypertrophy. There was a high ventricular septal defect measuring 13 mm. The aorta was dextroposed and over-riding. The aortic cusps were normal. The Eisenmenger complex was completed by the finding of a widened conus pulmonalis without any evidence of stenosis and with all pulmonary cusps normal. The wall of the right ventricle measured 10 mm. and was equal in thickness to the left ventricular wall. Otherwise there were normal heart findings.

Gross examination of the lungs showed no significant pathologic changes. Microscopically, there were no signs of pulmonary fibrosis. The capillaries were somewhat dilated. However, in the small and middlesized arteries there was a marked hyperplasia of the intima, in some vessels even so pronounced that the lumen was almost completely occluded (Fig. 3). The possible implications of these findings are discussed later.

Otherwise there were normal autopsy findings, including the kidneys that showed no signs of cystic degeneration.

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COMMENTS

As a rule, in Eisenmenger's complex the difference between systemic and pulmonary blood flow is small. The amount and the direction of the shunt is determined by the degree of aortic over-riding, the relation between systemic and pulmonary vascular resistance and the size of the septal defect. In the

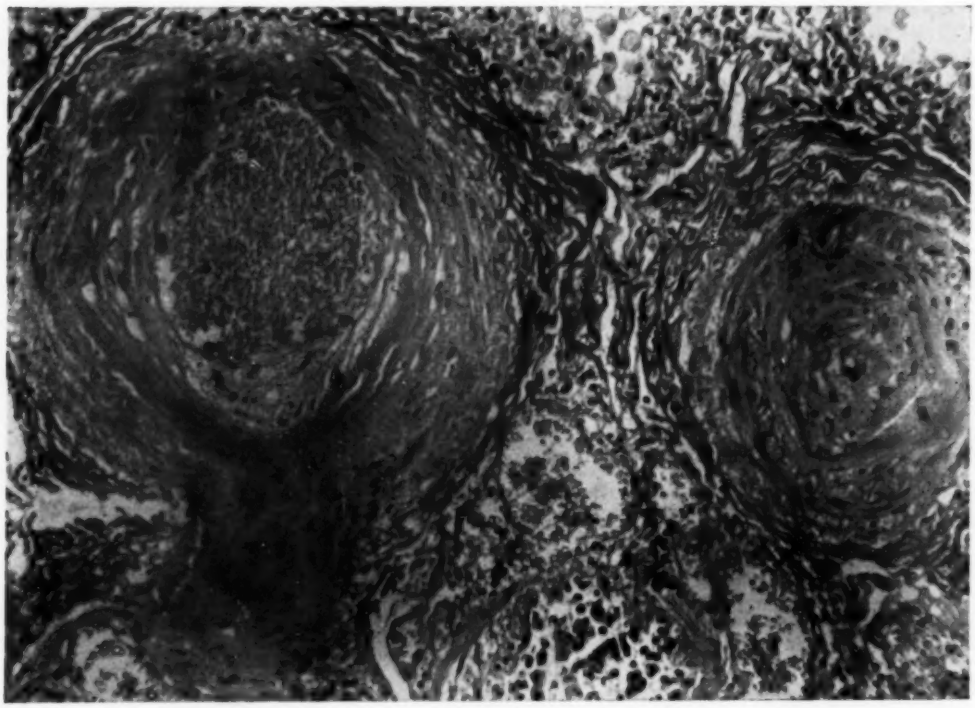

Fig. 3.—The microscopic picture of the pulmonary vessels. Note the advanced intimal hypertrophy in the arteries.

present case we do not know the direction of the intracardiac shunt. There are, however, reasons to believe that pulmonary blood flow was reduced because of diminished venous return to the right side of the heart, due to the drainage of the anomalous left caval vein into the arterial circulation, and furthermore because of the rather advanced dextroposition of the aorta. The microscopically recorded very advanced intimal changes in the pulmonary arteries indicate a high pulmonary vascular resistance favoring a diversion of the venous blood into the aorta. In Eisenmenger's complex x-ray examination of the lungs most often reveals an increase of the vascular shadows of the lungs, sometimes even showing marked hilar pulsations. In our case there were no such signs, which is easily explained by the above assumption of reduced pulmonary flow.

The differences of circulatory dynamics between this case and ordinary Eisenmenger cases, caused by the anomalous left-sided caval vein, may also explain the fact that this patient was a squatter, which is very rarely seen in connection with Eisenmenger's complex.

Another point of interest in this tragic case is the causal mechanism of death. The respiratory standstill occurred in the same moment as the tip of the catheter slipped into the anomalous caval vein. Autopsy revealed a small bleeding just in this region, surrounding the left vagus nerve. We hold it probable that the vagus nerve was stimulated by the pressure of the catheter. According to Pitts,[11] after stimulation of the central part of one vagus there is a latent period of decrease and finally an arrest of the discharge from the inspiratory center. This inhibition lasts as a rule for some time after the end of the vagal stimulation and then the discharge from the center reappears. In this case we hold it probable that the discharge from the respiratory center was interrupted and that reappearance of respiratory impulses failed on account of the patient's anoxemic state. A further sign of vagal stimulation was the initial vomiting attack. It is cousidered probable that the heart finally stopped as a sequel of myocardial anoxia.

SUMMARY

This is the report of a case of Eisenmenger's complex in a 10-year-old girl, associated with double superior venae cavae. The patient died during catheterization of the heart. The hemodynamics and the probable cause of death are briefly discussed.

SUMMARIO IN INTERLINGUA

Isto es le reporto de un caso del complexo de Eisenmenger associate con duple venas cave superior. Le patiente, un puera de 10 annos de etate, moriva durante catheterisation cardiac. Es presentate un breve discussion del hemodynamica in iste caso e del probabile causa del morte.

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FATAL MYOCARDITIS DUE TO EMETINE HYDROCHLORIDE

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LOS ANGELES, CALIF.

THERE are many reports of the cardiotoxic effects of emetine. By far the largest number describe changes in the heart rate, blood pressure, and electrocardiogram.

Klatskin and Friedman[1] in a study of ninety-three healthy young soldiers under treatment for intestinal amebiasis with emetine found that 83 per cent displayed some cardiovascular effect. Dack and Moloshok[2] have observed that the cardiac abnormalities may occur even after a course of emetine has been completed, and that in some instances the electrocardiographic manifestations persist for weeks.

Reports of human deaths due to emetine are exceedingly rare. Brown[3] in 1935 was able to find but ten cases. Two of these reports[4,5] are convincing, but although post-mortem examinations were done, descriptions of the heart were absent or inadequate. Kattwinkel's case[6] is the only report with electrocardiographic and detailed histologic observations. Otherwise descriptions of the myocardial lesions are limited to studies in experimental animals given varying amounts of emetine.[7,8]

The following case in which death occurred as a result of myocarditis during emetine therapy for amebic liver abscess is therefore described.

CASE REPORT

K.C., a 31-year-old white man, entered the hospital on Jan. 20, 1951, because of severe right upper quadrant pain and dyspnea. During the previous five months he had been hospitalized five times because of pain in the right flank, right upper quadrant of the abdomen, and back. During the six weeks before admission he had had fever, heavy sweats, loss of weight, and increasing abdominal and back pain. A few hours before admission, on turning over in bed, he was suddenly seized with severe pain in the right side of the thorax accompanied by dyspnea and a cough productive of brownish sputum.

The patient served in the Asiatic Theater during World War II and had had a persistent dysentery which was eventually diagnosed ulcerative colitis. He had not had bowel symptoms, however, in the two years prior to this hospital admission.

On physical examination, the patient was acutely and severely ill. The temperature was 103° F.; the heart rate, 130; respirations, 60; and the blood pressure, 130/60 mm. Hg. Signs of fluid were present over the lower half of the right thorax, and the right upper quadrant of the abdomen was very tender. Percussions elicited evidence of enlargement of the liver.

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The white blood count was 22,200 with 80 per cent polymorphonuclear cells. The red cell count was 3.76 million, and the hemoglobin was 10.8 grams per 100 c.c. The cephalin flocculation test was negative at 48 hours and the thymol turbidity was 3 units. Serum albumin was 3.3 grams, and the globulin 2.5 grams per 100 c.c. The chest film showed opacity of the lower one-third of the right lung field. The liver appeared to extend downward to the crest of the ilium in the film of the abdomen. Thoracentesis yielded 100 c.c. of thick lavender-colored nonodorous fluid which turned a milk chocolate color on standing. Smears and cultures of the fluid were negative for protozoa and bacteria.

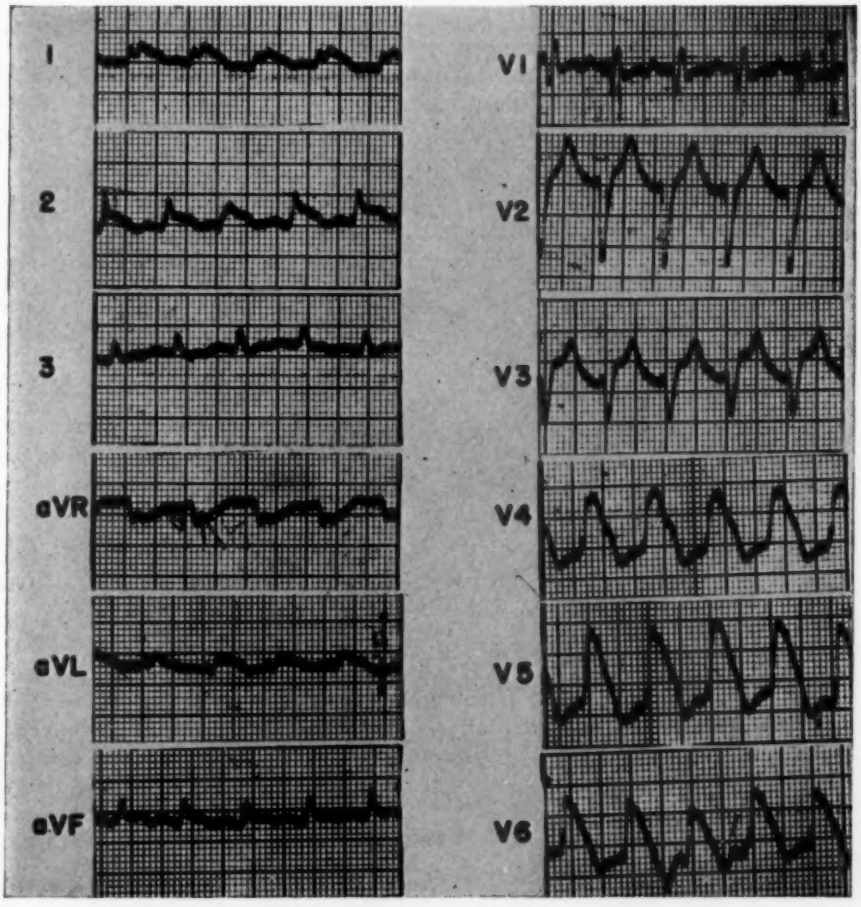

Fig. 1.—Electrocardiogram in a fatal case of myocarditis occurring during emetine hydrochloride therapy of amebic abscess of the liver.

Emetine hydrochloride, one grain (65 mg.) per day subcutaneously, Aureomycin, and Streptomycin were all started immediately. Within forty-eight hours the temperature had returned to normal. However, the patient continued to cough with production of thick violet-brown sputum. Repeated thoracenteses yielded large quantities of fluid which became dark amber in color and remained sterile on culture.

Emetine was discontinued on January 28, after 9 grains (0.585 Gm.) had been given. Despite the fact that his temperature remained normal, his general condition seemed to deteriorate gradually. A second course of emetine, one grain (65 mg.) per day subcutaneously was begun February 2, and continued for five days with a total of 6 grains (0.390 Gm.). The sputum became bile tinged, and fluid, although still evidently present, became impossible to obtain by thoracentesis. Accordingly, a thoracotomy was performed on February 10, and about 200 c.c. of thick,

purulent fluid was evacuated from the pleural space. Culture of this material produced *Pseudomonas aeruginosa*. The liver abscess was opened and drained through the diaphragm. A third course of emetine consisting of one grain (65 mg.) daily subcutaneously was begun on February 11, and continued for four more days for a total of five grains (0.325 Gm.).

After surgery the patient did rather poorly. He had considerable pain in the chest, coughed a great deal, and the wound drained large quantities of bile-stained material. His temperature remained virtually normal, however, and he was at no time considered critically ill. The blood pressure, which fell to a low of 80/60 mm. Hg immediately after surgery, returned to its previous normal level. On February 15, he complained of difficulty in breathing and required oxygen periodically. During the day he became much worse with marked dyspnea, cyanosis, tachycardia, and falling blood pressure.

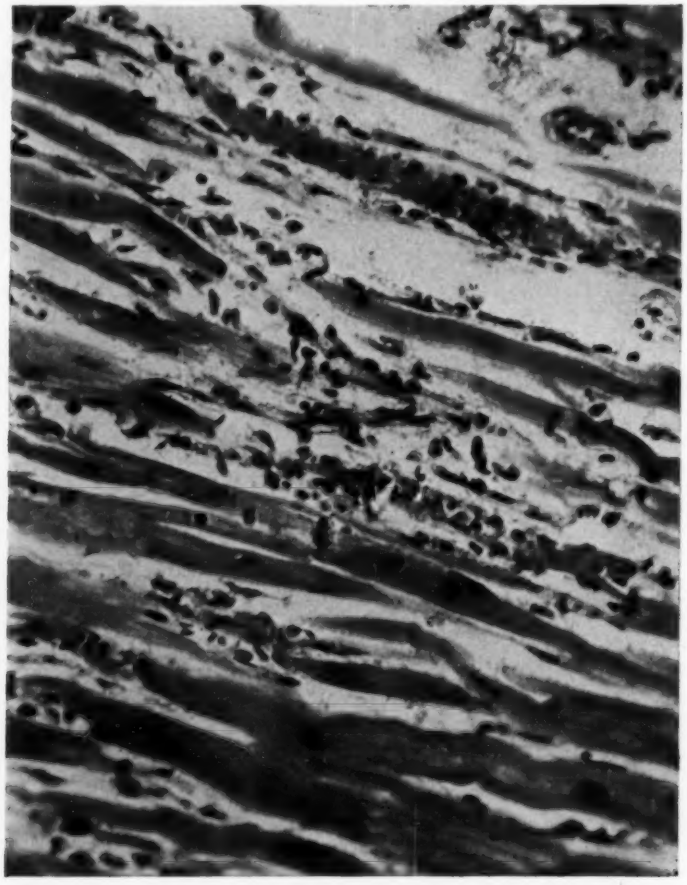

Fig. 2.—Histologic appearance of myocardium (×250; reduced ¼).

The electrocardiogram (Fig. 1) at this time showed a sinus tachycardia of 140. Voltage was low in the limb leads, and QRS complexes were slurred. The S-T segments were elevated in Leads I, II, aV_L, V_3, V_4, V_5, and V_6. In aV_R the S-T segment was noticeably depressed. The tracing was interpreted as representing severe myocardial injury.

All supportive efforts failed, and the patient died the afternoon of February 16, twenty-seven days after admission. He had had a total of 20 grains (1.3 Gm.) of emetine hydrochloride during this period.

NECROPSY REPORT

(Limited to pertinent findings)

Gross Examination.—

Lungs: The right lung was bound to the chest wall and diaphragm by dense, tough adhesions. A poorly demarcated, thick-walled abscess cavity was present in the lower chest bounded by the lower lobe of the lung, the diaphragm, and the chest wall. No major bronchial communication with the cavity could be identified. The remainder of the lung showed marked congestion and areas of atelectasis.

Liver: The liver weighed 2,000 grams. Its posterior-superior surface was firmly adherent to the diaphragm, and on section a single irregularly shaped abscess cavity 3 cm. in diameter was found in this area. The abscess contained necrotic but not purulent material. Its wall was grayish-yellow and in places measured 0.5 cm. in thickness. The liver elsewhere and the biliary tract appeared normal.

Heart: The heart weighed 350 grams. The pericardium and endocardium were smooth and translucent, and the valve orifices and leaflets were normal. The ventricular muscle was of normal thickness and on section presented the usual reddish-brown color. The coronary arteries were widely patent, and only minimal atherosclerosis was present.

Gastrointestinal tract: No ulcerations, erosions, or hemorrhages were found in any part of the gastrointestinal tract.

Microscopic Examination.—

Liver: Trophozoites of *Endamoeba histolytica* were seen in the wall of the abscess. Sections from other areas of the liver showed rather extensive infiltration of the portal triads with inflammatory cells predominantly lymphocytes. There was also some central necrosis of the hepatic cell cords.

Heart: All sections showed evidence of an interstitial myocarditis varying in degree in different areas (Fig. 2). In the more seriously involved areas, there were separation of muscle fibers and infiltration of the interstices by atypical cells, most of which resembled histiocytes. Only occasional polymorphonuclear leukocytes were seen. Many of the extraneous cells had "caterpillar nuclei" and resembled the Anitschkow myocyte or cardiac histiocyte. Definite evidence of destruction of the myocardial fibers was likewise seen. Where this was present, the nuclei were pyknotic and at times assumed bizarre appearances. The striking finding was the relative absence of inflammatory cells. In the sections studied neither the epicardium nor endocardium was involved.

Comment.—The most striking finding in this case is the presence of extensive destruction of the myocardium by an apparent interstitial myocarditis. The cells present in areas of necrosis were mainly histiocytes. The exact nature of the myocarditis cannot be definitely stated. It has the appearance, however, of a toxic rather than an inflammatory lesion.

DISCUSSION

That the myocarditis found in this case was due to emetine might be debated. The patient was afebrile after the first two days, however, and displayed no clinical features of other diseases usually associated with myocarditis. At post-mortem examination no other cause for the myocarditis was found. Furthermore, the histologic picture of the myocardium was similar to that seen in experimental animals given emetine.

The toxic dose of emetine in humans is subject to considerable variation. Some individuals show electrocardiographic changes after a single dose of one grain of emetine while others tolerate a full ten-day course with no sign of intoxication. It is excreted very slowly and is probably not metabolized, hence it has strong cumulative properties. The minimal lethal dose for man has been calculated from animal studies as approximately 20 mg./kg. of body weight[8] or one grain per day for 21 days.[9] The two reports in which this information is available[4,5] support this figure, as does ours. Kattwinkel's case, however, had only 0.75 Gm. over eleven days. The weight of this case is not recorded. The fatal cases cited by Brown[3] received between 1.04 Gm. and 2.64 Gm. in 2 to 8 weeks. Our patient whose weight was 147 pounds (67 kg.) received a total of 1.30 Gm. (20 grains) in 27 days, amounting to 19 mg./kg. It is of incidental interest that easily recognized trophozoites of *Endamoeba histolytica* were still present in the wall of the liver abscess despite the relatively large quantity of emetine.

In amebic abscess, the seriousness of the disease and urgency of the situation often result in emetine being given in longer or more frequent courses than is desirable, and evidences of toxic effects in the electrocardiogram are not infrequent. Although reports of fatalities from emetine are very few, death from amebic abscess of the liver during the course of treatment is not rare. It is possible that the contribution of emetine to the fatalities has been overlooked. Such was the case in this instance until a careful review of the patient's record and of the pathologic findings disclosed the etiologic relationship of the emetine. This finding led to a review of twenty-five cases of amebic abscess of the liver coming to necropsy. Among these were two cases that died of sudden unexpected cardiac failure with rapid onset of dyspnea, cyanosis, and falling blood pressure after having been treated with emetine. One was a 54-year-old male with rupture of an amebic abscess into the right pleural cavity. Thoracotomy and drainage were performed. He received a total of 25 grains (1.62 Gm.) of emetine in repeated courses over 63 days. The other was a 55-year-old Negro woman with an amebic liver abscess proved by aspiration and the finding of trophozoites in the material. She received 14 grains (0.91 Gm.) in two courses over 16 days. Between courses the electrocardiogram showed low voltage of QRS complexes and low T waves in all leads.

The necropsies in these two cases confirmed the diagnosis of amebic abscess of the liver, but failed to disclose a reason for the sudden cardiovascular collapse and death. The microscopic descriptions of the hearts were inadequate. It seems quite possible, however, that emetine-induced myocarditis was present in both.

It is fortunate that Conan[10,11] applied the relatively innocuous drug chloroquine to hepatic amebiasis. His striking success has been amply confirmed by many investigators. Chloroquine is equally, if not more, effective than emetine in the treatment of hepatic amebiasis, and should replace it largely in the therapy of this lesion. Emetine will continue to be useful, however, in other extraintestinal lesions of amebiasis and the occasional chloroquine fast liver abscess,

and hence cannot as yet be discarded completely. It is therefore well to recognize and respect the potential hazards involved in its use.

SUMMARY

1. Emetine hydrochloride when given in the usual therapeutic doses frequently produces definite but not dangerous effects on the heart.

2. Individual tolerance to emetine toxicity is extremely variable. The human lethal dose appears to be about 20 mg./kg. of body weight.

3. Long or frequently repeated courses of emetine may constitute a distinct hazard. An illustrative case of emetine-induced myocarditis with death and pathologic findings is described.

4. Although chloroquine should replace emetine in the therapy of hepatic amebiasis, the latter will still be useful in other forms of extraintestinal amebiasis. The potential hazards of its use should therefore be recognized.

SUMMARIO IN INTERLINGUA

Es presentate le caso de un amebic abscesso hepatic in que occurreva un subite inexpectate collapso cardiovascular e morte post 26 dies de tractamento intermittente con hydrochlorido de emetina. Nos describe le cambiamentos electrocardiographic e le anormalitates histologic constatate. Es mentionate 2 altere casos presumptive de subite collapso e morte occurrente durante un therapia a emetina. Nos summarisa brevemente le qualitates cardiotoxic de emetina e le problema del calculation de su dose mortal.

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Announcements

A three-day International Symposium on ENZYMES: UNITS OF BIOLOGICAL STRUCTURE AND FUNCTION, sponsored by the Henry Ford Hospital and The Edsel B. Ford Institute for Medical Research will be held in the auditorium of Henry Ford Hospital, Nov. 1, 2, and 3, 1955.

Interrelationships between enzymology and other fields, notably genetics, physiology, biochemistry, and pharmacology, will constitute the general theme of the Symposium. The specific topics for the six sessions will be: Origin of Enzymes, Status of the Gene-Enzyme Relationship, Enzymes and Cell Structure, Enzymatic Basis of Some Physiological Functions, Cellular Energy Sources, and Regulation of Enzyme Activity. More than thirty internationally known scientists have accepted invitations to participate. Interested persons may secure a copy of the Preliminary Announcement by writing to Dr. Clarence E. Rupe, Henry Ford Hospital, Detroit 2, Michigan. Invitations will be sent to as many as can be accommodated.

Applications for awards available July 1, 1956, will be received by the LIFE INSURANCE MEDICAL RESEARCH FUND as follows: (1) Postdoctoral research fellowships, until October 15, 1955. Preference is given to those who wish to work on cardiovascular function and disease or related fundamental problems. Minimum stipend $3,600, with allowances for dependents and necessary travel; (2) grants to institutions in aid of research on cardiovascular problems, until November 1, 1955. Support is available for physiological, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field. Predoctoral fellowships will not be offered by the Fund this year. Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 East 46th Street, New York 17, N. Y.

The VERMONT HEART ASSOCIATION in cooperation with the UNIVERSITY OF VERMONT COLLEGE OF MEDICINE plans to organize two seminars in heart disease in September, 1955, in Burlington, Vermont. The seminar on FUNCTIONAL AND DEGENERATIVE HEART DISEASE will be given by Dr. W. Raab, Professor of Experimental Medicine at the University of Vermont, and Head of the Cardiovascular Research Unit of the University of Vermont at the Bishop DeGoesbriand Hospital, on September 14 and 15. A seminar on the ELECTROCARDIOGRAPHIC DIAGNOSIS OF AURICULAR AND VENTRICULAR HYPERTROPHY AND STRAIN will be given by Dr. E. Lepeschkin, Associate Professor of Experimental Medicine, Chief Cardiographer of the Bishop DeGoesbriand Hospital, and Established Investigator of the American Heart Association, and Dr. B. Surawicz, Instructor of Medicine and Research Associate in Experimental Medicine at the University of Vermont, on Sept. 16 and 17. Dr. R. P. Grant of the National Heart Institute and Dr. E. Cabrera of the National Institute of Cardiology in Mexico City will be among the guest speakers.

THE 38TH ANNUAL OCCUPATIONAL THERAPY CONVENTION will be held in San Francisco, Calif., Oct. 25-28, 1955, at the Sheraton-Palace Hotel. The theme of the convention is "Bridges to the Future." Outstanding leaders in various medical and allied fields will present current trends and problems in the fields of orthopedics, neurology, and psychiatry, as well as tuberculosis, geriatrics, and pediatrics.

Preceding the convention there will be a Workshop Institute (Oct. 24-25) highlighting "The Patient's Point of View." A panel of speakers representing various social-medical-educational fields will open the meeting, followed by discussion workshops.

Any interested individual or group may obtain further program and convention information by writing to Northern California Occupational Therapy Association, 1680 Mission Street, San Francisco, Calif.